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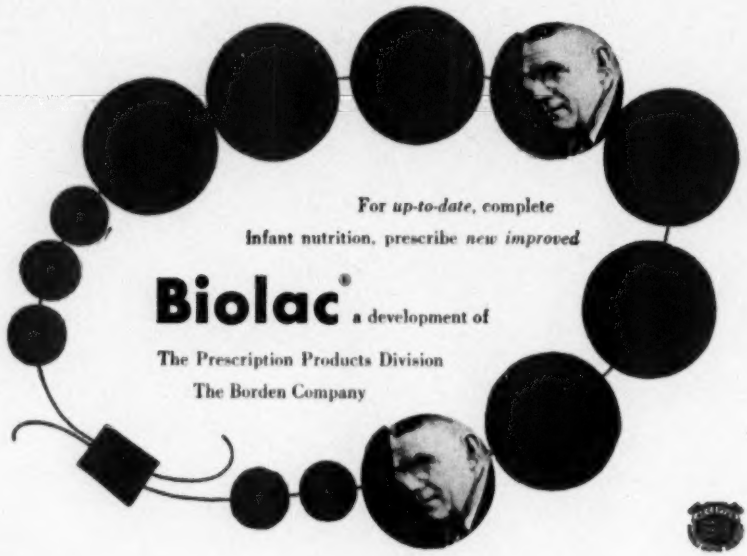

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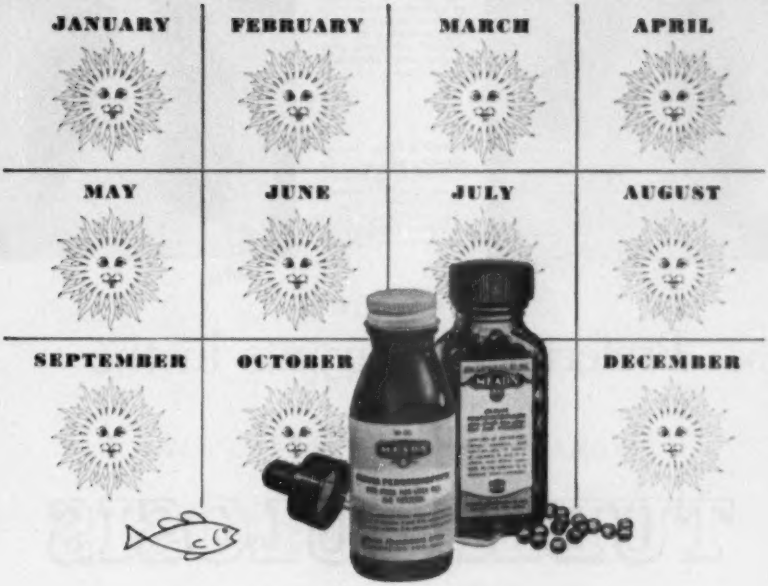

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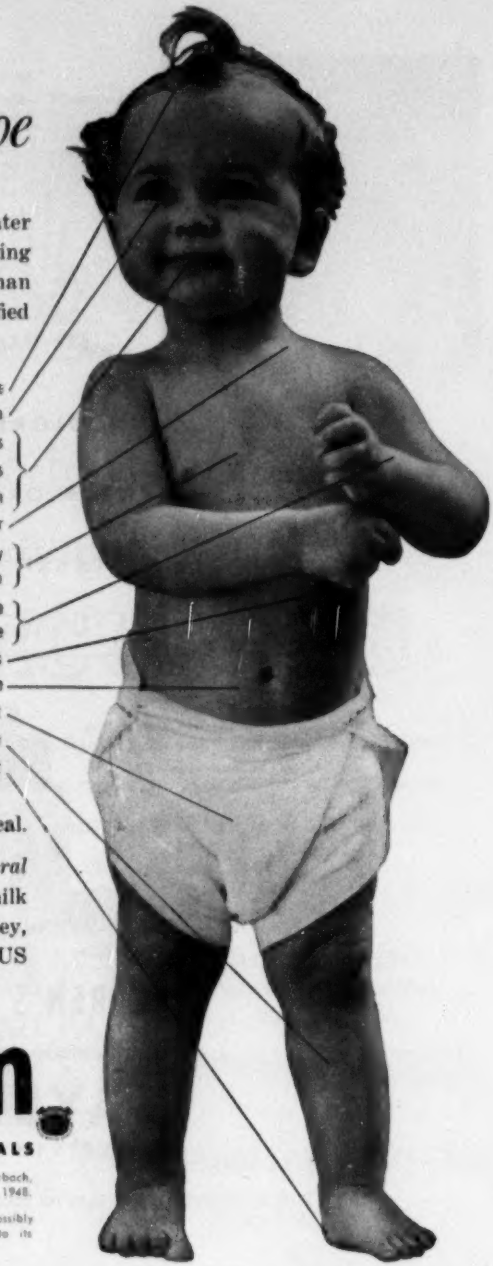

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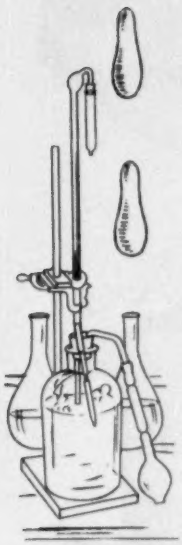

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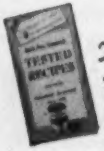
[1]Gamble, J. A.; Hill, N. R. and Bosley, A. K., U. S. Dept. of Agric. Tech. Bull. No. 671, page 61, (March 1939).



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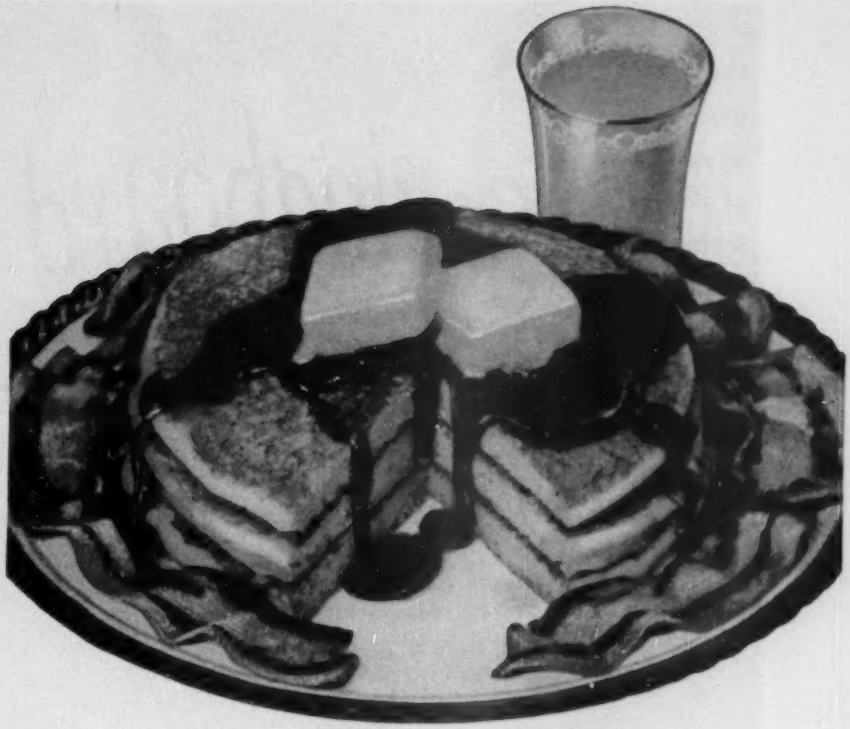

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(1) Thorn, G.W.; Quinby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
(2) Orent-Keiles, E., and Hallman, L. F., Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

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references: 1. Jeans, P.C. and Marriott, W.M.: Infant Nutrition, Mosby, 4th ed., 1947
2. Rose, M.S.: Rose's Foundation of Nutrition, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944
3. Sherman, H.C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946

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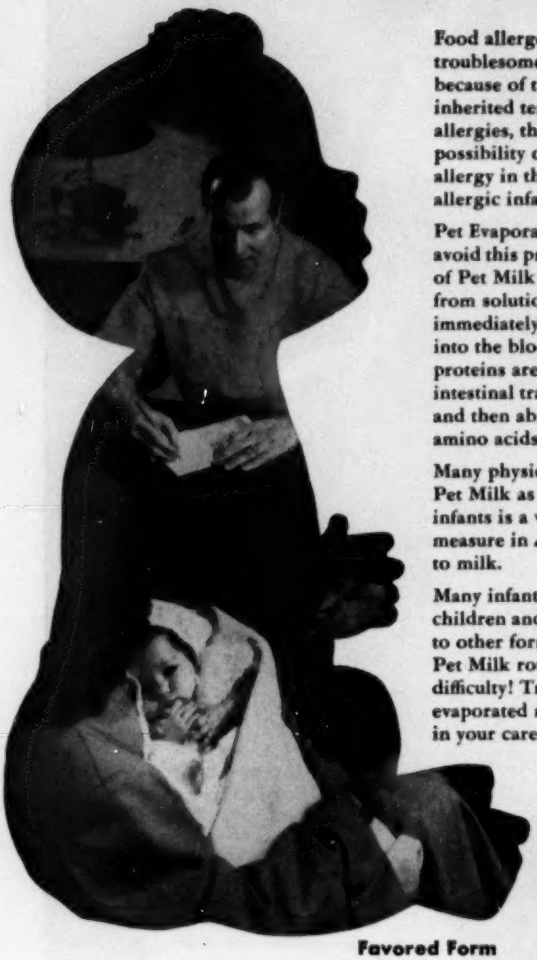

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VOLUME 80 OCTOBER 1950 NUMBER 4

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TREATMENT OF PRIMARY ATYPICAL PNEUMONIA IN CHILDREN WITH AUREOMYCIN

Report of Nineteen Cases

CHARLES E. ANDERSON Jr., M.D.
SHREVEPORT, LA.

MUCH has been written about, and much discussion has ensued with regard to, the disease termed atypical nonbacterial primary pneumonia, or virus pneumonia, its etiology and treatment. Most of the discussion has dealt with etiology, and I wish to make it quite clear in the beginning that the etiologic agent in the present series of patients studied is certainly not proved or disproved. I have purposely omitted the term "virus pneumonia" and substituted "primary atypical pneumonia," admitting without hesitation that the question, "Why is this called primary atypical pneumonia, cured with aureomycin?" cannot be answered satisfactorily.

The ambiguous status of the etiology of this disease is still well characterized by the designation recommended early in the war by the Army Epidemiological Board, namely "primary atypical pneumonia, etiology unknown." [1] The viral nature of the etiologic agent is strongly suggested by the transmissibility of the disease to normal persons by means of bacteriologically sterile filtrates of sputum from patients with active disease.[2] Furthermore, the finding of certain strains of nonhemolytic streptococci in cultures of material from lungs and sputum of a number of patients with this disease and the demonstration of agglutinins for these streptococci during convalescence in a significant proportion of patients suggests a possible synergism of such bacteria and some unknown virus in the causation of the disease.[3]

From the Children's Clinic.

Read at the meeting of the Louisiana State Pediatric Society, Shreveport, La., Jan. 8, 1950.

1. Primary Atypical Pneumonia: Etiology Unknown, Official Statements, War Med. **2**:330-333, 1942.

2. Transmission of Primary Atypical Pneumonia to Human Volunteers, Commission on Acute Respiratory Diseases, Bull. Johns Hopkins Hosp. **79**:97-167, 1946.

3. Horsfall, F. L., Jr.: Primary Atypical Pneumonia, New York State J. Med. **46**:1810-1814, 1946.

The diagnosis of primary atypical nonbacterial pneumonia is based chiefly on the following criteria: First, the onset is usually gradual, with nonproductive cough, fever, and less general malaise than would be expected. The cough progressively increases in severity and is particularly severe at night, and most of the symptoms are typical of an infection of the upper respiratory tract. Second, physical examination reveals rather minimal signs in the chest, most frequently rales, which are less than would be expected from the roentgen evidence of pulmonary consolidation. Third, laboratory examinations usually show a low to normal leukocyte count, and examination of bronchial secretions demonstrates the usual bacterial flora. Fourth, serologic studies on serial serum specimens do not reveal the development of antibodies for recognized viral or rickettsial agents. Fifth, treatment with sulfadiazine or penicillin does not produce clinical or objective improvement in the patient with an uncomplicated disease. Sixth, the appearance in the serum of patients of cold hemagglutinins for human group O cells or agglutinins for Streptococcus M G during the course of the disease or in convalescence has been noted in a variable proportion of patients in a different series. In the private practice of pediatrics, the average laboratory is unable to carry out the serial serologic studies or the agglutination tests; therefore these criteria were not included in this series.

Until recently, it was generally agreed that no effective therapy existed for primary atypical pneumonia. The sulfonamides and penicillin are apparently ineffective against the disease unless they might influence bacterial complications, which are quite uncommon. Streptomycin also has been found ineffective. Convalescent serum does not offer a practical therapeutic approach, and even the favorable reports of its use are not entirely convincing.

The discovery of aureomycin,[4] an antibiotic agent which is highly effective against infections due to known rickettsias and the viruses of the psittacosis–lymphogranuloma venereum group in animals and in those human patients who have been observed to date, is of particular interest in relation to primary atypical pneumonia. The manifestations of psittacosis and Q fever infections in man are often virtually indistinguishable from those of primary atypical pneumonia, in which the etiologic role of these or any other known agents can be ruled out.[5] Moreover, other rickettsias, such as those which cause epidemic typhus and are not usually thought of as causes of pneumonia, may produce symptoms and pulmonary lesions which are distinguishable from those of primary atypical pneumonia only by specific serologic tests or by

4. Aureomycin—A New Antibiotic, Ann. New York Acad. Sc. **51**:175-342, 1948.

isolation of the rickettsias.[5] It seems quite possible, therefore, that an unidentified agent or agents of this kind may cause some of the cases now classified as instances of "primary atypical pneumonia, etiology unknown."

For such reasons, shortly after aureomycin became available it was used in the treatment of so-called primary atypical pneumonia, and the reports were quite gratifying. The wide range of activity of aureomycin and its relatively low toxicity served to minimize the hazards of a clinical trial with this agent, which had been effective in vitro and in vivo against a large variety of gram-positive and gram-negative bacteria, including those which commonly cause pneumonia.

The reports on treatment of primary atypical pneumonia with aureomycin have dealt mainly with adults. Recently, reports have been published concerning the use of aureomycin in the treatment of various types of pneumonia in children.[6] Included were a few cases in which the diagnosis of atypical pneumonia was established by the criteria mentioned above.

Of the 9 cases falling into the category of atypical pneumonia, 5 fulfilled all the criteria, including serologic confirmation. The age range was 2½ to 11 years, and temperatures ranged from 101 to 105 F. The infections were classified as severe in 1 case, moderate in 2 and mild in 2; none of the patients required oxygen. Leukocyte counts varied from 7,000 to 11,000 cubic millimeter, and 4 of the 5 patients had cold agglutinin titers ranging from 1:64 to 1:2,048, whereas the Streptococcus M G titers varied between 1:20 and 1:640.

Aureomycin therapy was instituted from four to nine days after the onset of illness. Four of the patients showed a favorable response and became afebrile 36 hours after therapy was started. Roentgenologically, however, the pneumonic process was found to resolve more slowly than in the cases of bacterial pneumonia. The fifth patient required 4½ days for defervescence, and this case was regarded as a probable therapeutic failure.

The present report is concerned with treatment of 19 children, all of whom had typical infection of the upper respiratory tract with cough, roentgen evidence of pneumonitis, leukopenia in most instances and invariable increase in lymphocytes. Bacterial floras were normal, and all patients had two to three days' treatment with sulfadiazine and/or penicillin, despite which therapy they were clinically worse or unimproved.

---

5. Finland, M.; Collins, H. S., and Wells, E. B.: Aureomycin in the Treatment of Primary Atypical Pneumonia, New England J. Med. **240**:241-246, 1949.

6. Olshaker, B.; Ross, S.; Recinos, A. Jr., and Twible, E.: Aureomycin in the Treatment of Pneumonia in Infants and Children, New England J. Med. **241**:287, 1949.

All 19 children were mildly to moderately ill. Chest pain and dyspnea were absent in all instances and general fatigue and malaise not too pronounced. The children were actually up and about, not feeling too bad at the time the initial roentgenogram was taken.

With one exception, the roentgen manifestation of the disease was a rather fan-shaped infiltration in the bases of one or both lungs. There was no diffuse mottling, and the migration so often mentioned in adults with this disease was not noted.

Treatment other than use of aureomycin included only steam, acetylsalicylic acid and syrup of dihydrocodeione bitartrate for the nocturnal cough. The last-named drug seemed most efficacious and was tolerated well.

There were no complications of any type in this series.

Following are reports of typical cases.

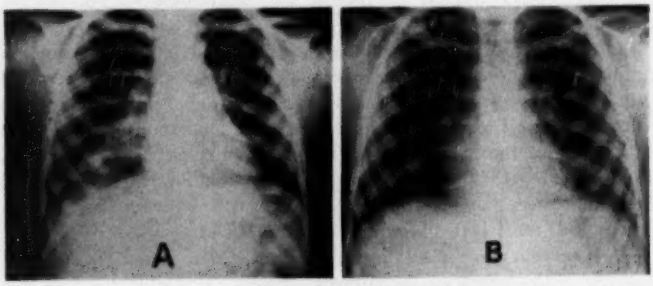

Fig. 1.—*A*, pneumonitis at the base of the right lung, June 6. *B*, about 50 per cent improvement, June 15.

REPORT OF CASES

CASE 1.—J. R., a 4 year old girl, was seen June 6, 1949. There had been fever of four days' duration, the temperature varying from normal in the morning to 102.5 F. in the evening. A dry, hacking cough, severer at night, had been present for 36 hours. On June 3, three days prior to admission, administration of pansulfa® (equal parts of sulfadiazine, sulfamerazine and sulfathiazole) was started in doses of about 1 Gm. per pound (0.5 Kg.) per 24 hours, distributed in four hour doses, prescribed by telephone because of fever and sore throat. At the end of three days, with progressively increasing cough and continued fever, the child was brought to the office. Examination revealed a well developed, well nourished little girl, who did not appear to be very ill. The pharynx was red, and the nose showed slight coryza. The chest was resonant, but the breath sounds were coarser on the right side, and there was a questionable rale in the base of the right lung despite shallow breathing. The roentgenogram (fig. 1*A*) showed pneumonitis at the base of the right lung. On this date her white cell count was 6,000. Cultures were made from nasal and bronchial secretions after frequent gagging and coughing. She was given aureomycin, 120 mg. every four hours for the first 24 hours, then every six hours, and syrup of dihydrocodeione bitartrate for the cough. Bed rest, acetyl-

salicylic acid and general symptomatic treatment were advised. On return, June 9, she had been free of fever for the previous twenty-four hours, had less cough and was feeling well. A roentgenogram on this date (fig. 1 *B*) revealed about 50 per cent improvement. Medication was discontinued, and by June 15 the roentgenogram showed complete clearing of the pneumonitis.

CASE 2.—C. P., a 5½ year old girl, was seen at home on Nov. 9, 1949, because of sudden temperature elevation with no other signs or symptoms. The examination at this time revealed a slightly infected pharynx, not too significant, and nothing else of note. She was given penicillin orally, 100,000 units every two hours during the day and every three hours at night, on an empty stomach, with acetylsalicylic acid and symptomatic treatment. On the following day a mild hacking cough developed. She was seen in the office on Nov. 12, with a persistent fever (temperature reaching 103 F.), increased cough, general malaise and some aching. She was unquestionably sicker than when seen at home, despite two full days of penicillin therapy. Examination at this time revealed slight evidence of an infection of the

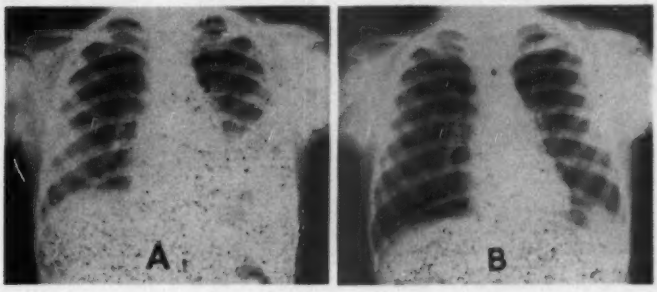

Fig. 2.—*A*, infiltration in the base of the left lung, November 18. *B*, practically complete clearing, November 18.

upper respiratory tract, with fine, crepitant rales in the base of the left lung. A roentgenogram (fig. 2 *A*) demonstrated infiltration in the base of the left lung. The leukocyte count was 6,150. After nasal and bronchial secretions were obtained for culture, administration of aureomycin was begun, 200 mg. every six hours. She returned November 18, six days later, with a history of having had no fever after two days, coughing less and feeling quite well. A roentgenogram taken on this date (fig. 2 *B*) showed practically complete clearing. This child's cough subsided slowly over a period of about 10 days.

CASE 3.—M. Y., a 2½ year old girl, had a mild "head cold" on April 3, 1949, with very little cough and temperature reaching 100 to 101 F. Because of persistent fever she was seen at the office on April 7, with a generalized infection of the upper respiratory tract. She was still coughing but her chest was clear on examination. She was given an injection of 300,000 units of penicillin intramuscularly, this being the so-called ninety-six hour penicillin. This was repeated on April 9, although the child was not seen at this time. She was returned to the clinic on April 11, with a temperature of 102 F. two or three times daily, listless and coughing a good deal more than previously, and at this time both lungs were filled with fine crepitant

rales. The child appeared sicker. A roentgenogram (fig. 3 *A*) revealed considerable pneumonia bilaterally. The blood cell count showed 7,850 leukocytes, and bronchial and nasal secretions were cultured. She was given 100 mg. of aureomycin every four hours for the first 48 hours and then every six hours thereafter. The temperature subsided to normal in 36 hours, and the cough lasted four days. Roentgen examination, repeated four days later, showed remarkable clearing of her pulmonary fields (fig. 3 *B*).

In the table are given specific data on the entire group of children. The average duration of illness before aureomycin was begun was 3.7 days. Of these 3.7 days, 2.4 days were utilized in treatment of the infection with penicillin and/or sulfonamides.

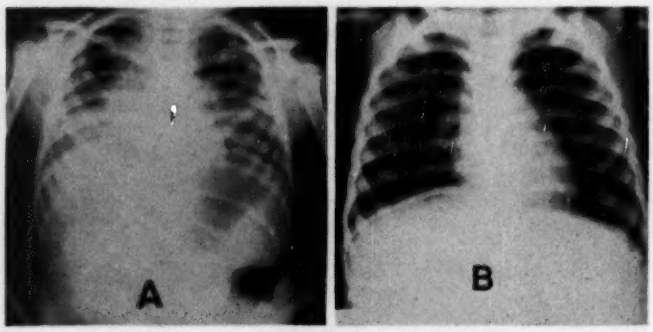

Fig. 3.—*A*, considerable pneumonia bilaterally, April 4. *B*, remarkable clearing of the pulmonary fields, April 20.

Aureomycin was given over an average period of four days. Temperature elevation persisted for an average of two days after administration of aureomycin was started. Cough persisted for 5.4 days as an average, and roentgen findings persisted for an average of 5.7 days.

Although no control series is available in this study, I am convinced that this group of 19 children were noticeably benefited by aureomycin, particularly in regard to duration of symptoms and roentgen findings.

SUMMARY

The cases of 19 children with primary atypical pneumonia are presented which fulfil all the criteria for diagnosis except serologic studies on serial serum specimens for antibodies against recognized viral or rickettsial agents and studies for development of cold hemagglutinins. Clinical and roentgen response to treatment with aureomycin following failure to respond to either penicillin and/or sulfonamides is shown both

Summary of Data in Nineteen Cases

Patient	Age, Yr.	Duration of Symptoms, Days	Previous Therapy		Leukocyte Count	Roentgenogram	Aureomycin Therapy			Duration of Fever After Aureomycin Started, Hr.	Duration of Cough, Days	Number of Days Before Roentgenogram Cleared
			Drug	Days			Duration, Days	Amount, Mg.	Interval, Hr.			
J. L.	5	6	Sulfonamide	3	9,050		3	150	4	36	3	4
A. P.	8	4	Sulfonamide and penicillin	2	5,700		3	200	6	24	3	5
B. F.	2	4	Penicillin	2	7,500		6	100	6	12	4	4
K. C.	6	6	Sulfonamide	3	6,550		3	165	6	38	3	4
C. A.	1½	4	Sulfonamide	3	7,550		4	50	4	24	7	6
M. Y.	2½	6	Penicillin	2	7,850		5	100	4	36	4	4
J. R.	4	4	Sulfonamide	2	6,100		4	120	4	48	4	9
L. M.	5½	3	Penicillin	2	10,300		3	165	4	48	4	7
S. B.	1½	7	Sulfonamide and penicillin	4	8,000		4	100	4	48	5	7
A. H.	4½	5	Sulfonamide	3	7,300		4	135	4	72	7	5
P. C.	3	4	Penicillin	2	10,650		3	100	4	24	2	6
J. T.	¾	3	Penicillin	3	9,550		4	60	4	72	10	5
J. H.	4	3	Sulfonamide	2	8,000		3	165	4	48	3	5
L. A.	10	3	Penicillin	2	4,700		5	200	4	72	5	8
C. P.	5	2	Penicillin	2	6,150		4	200	6	48	10	3
J. C.	5	2	Penicillin	2	4,550		4	200	6	72	7	8
D. S.	7	4	Penicillin and sulfonamide	2	10,300		5	100	6	36	5	8
S. H.	5	7	Sulfonamide	3	7,400		4	200	6	18	10	5
J. P.	8	5	Sulfonamide and penicillin	4	4,200		5	150	6	96	7	6

by three case histories and two charts, which summarize findings in the 19 cases, and by roentgenograms of pneumonic lesions before and after therapy. Certainly in this series of cases of children with pneumonia there seems to be no doubt that aureomycin was not only of marked benefit but that its effect was rather dramatic in some instances. It is admitted that proof of the etiology of these pneumonias may be questioned; however, they fulfil all the criteria other than those mentioned above in regard to serum studies. The facilities for the latter are not available in the average pediatric clinic engaged entirely in private pediatric practice.

No effort is made to clarify the etiology of primary atypical pneumonia.

TESTING OF TREND IN BODILY DEVELOPMENT OF SCHOOL CHILDREN

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MUCH interest has been taken lately in the changing growth rates in school children. Daley [1] gave a detailed report on heights and weights recently obtained from various London districts, and Spies and his co-workers [2] published an account on the determination of status and progress in children with nutritive failure. Spies and his associates based part of their findings on Wetzel's grid, which is similar to that described by one of us [3] elsewhere. Trends of growth may, of course, be estimated by calculating the means of height and weight at each age, or weights for each height, irrespective of age, but many more children than are generally to be found in one school would be needed in order to arrive at a definite estimate. In the following a method is described by which the medical officer, without much labor and arithmetic, may easily test the trend in single schools under his supervision.

In the present case, it was desired to learn whether conditions incident to the siege of Jerusalem influenced the development of a group of school children who were known to us from a previous investigation.

As will be remembered, unrest in this country developed after the end of the second World War. Hostilities started with the United Nations' declaration on the establishment of a Jewish State (Nov. 29, 1947). The food situation in Jewish Jerusalem deteriorated as the only road from the coast gradually became obliterated, and the last supplies reached the city by April 1948. Arab forces started shelling on May 1, and an open war raged within the city until June 11, which brought the

From the Department of Hygiene, Hebrew University.

1. Daley, A.: Heights and Weights of London School Children, M. Officer **79**:242-244 (June 5) 1948.

2. Mann, A. W.; Dreizen, S.; Spies, T. D., and Pyle, S. I.: The Determination of Status and Progress in Children with Nutritive Failure, J. Pediat. **31**:161-171 (Aug.) 1947.

3. Koch, W.: Height, Weight, and Age Charts for Children of School Age: A Simplified Method of Computation, J. Roy. San. Inst. **17**:120-128 (March) 1947.

cease fire order. A few days prior to this date food came in via an alternative road, and then the situation rapidly improved. The acute shortage during which people had to subsist on their lean rations and stocks lasted about six to seven weeks, a period which was followed by one of ample and regular supplies.

Regular growth in children proceeds by a simultaneous increase in height and weight, leading to an increase in the surface area of the body. Let us, for example, consider a girl, age 11 years, whose height is 130 cm. and whose weight is 30 Kg. There are three ways by which she may reach the surface area of a 12 year old girl.[3] First, the normal one, by putting on about 3.5 Kg. of weight and about 5.5 cm. of height; second, by a 6 Kg. weight increase without any change in height and, third, by a 12 cm. height increase without increase in weight. Obviously, while the regular simultaneous increase in both height and weight would leave her physique unchanged, putting on weight alone would make her too fat, and an increase solely in height would make her too lean. Any attempt to estimate the progress made has therefore to be based on two criteria: (*a*) whether there is a proper increase in surface area (that is, whether the number of children falling above or below their appropriate age standard has changed as compared with previous years) and (*b*) whether the height-weight relation has remained the same (that is, whether the distribution of children within the channels has changed).

An answer to the first question, namely, maintenance of proper growth in surface area, is readily obtained from a chi-square test performed with use of a fourfold table. Before the outbreak of the war (1947) 56 children in our sample fell below their respective age standard and 61 above; the corresponding values obtained at the turn of 1948-1949 were 48 below and 84 above.[4] A slight improvement during the year may be suspected, since 48.2 per cent of the children were below standard in 1947 but only 36.2 per cent in 1948-1949. Using a fourfold table of the type

	Below Age Standard	Above Age Standard	
1947	a	b	$a+b$
1948-1949	c	d	$c+d$
	$a+b$	$b+d$	$a+b+c+d$

and inserting our actual values, we obtain

1947	56	61	117
1948-1949	48	84	132
	104	145	249

The formula for computing chi-square from such a fourfold table is

$$\chi^2 = \frac{(ad - bc)^2 \times (a + b + c + d)}{(a + b) \times (b + d) \times (a + b) \times (c + d)}$$

or

$$= \frac{(56 \times 84 - 61 \times 48)^2 \times 249}{104 \times 145 \times 117 \times 132} = 3.37.$$

4. All children in the 1947 sample were contained in the 1948-1949 sample as well.

From any table or chart of the distribution of chi-square [5] it is found that the chi-square would have to be at least 3.84 in order to reach significance (p=0.05) and that 3.37 would correspond to p=0.07, which is slightly below the level of significance.

The tentative answer at this stage is that the children showed a rather better development in 1948-1949 than in 1947, but that this improvement is not definitely significant; no inference can, however, be drawn as to whether they retained their physique or grew fatter or thinner.

The latter information is obtained by testing the height-weight relation, that is, the channel distribution, in 1947 and 1948-1949. The procedure is given in the following tabulation:

Channel	1947*	1948/1949 Observed	1948/1949 Expected	$c-d$	Squares of e	f/d
a	b	c	d	e	f	g
— III	23	50†	22.30	+30.80	948.64	33.64
— II	16	25	18.05	+ 6.95	48.30	2.68
— I	35	23	29.49	—16.49	271.92	6.89
+ I	23	15	25.96	—10.96	119.90	4.62
+ II	11	6	12.41	— 6.41	41.09	3.31
+ III	7	4	7.90	— 3.90	15.21	1.93
	117	132	132.00	0.0 ‡		53.07

* Data are included in column b for only those children whose data were available for 1948-1949 as well.

† The number 50 includes also children falling below channel — III.

‡ The total of values in column e should be very nearly 0; the sum may differ slightly from 0, however, because decimals are calculated to only two places.

Column a indicates the channels as shown in a previous publication.[5] Channels —III and —II should each contain 12.5 per cent of those considered lean in a normal population, channels —I and +I each 25 per cent (neither lean nor fat) and channels +II and +III each 12.5 per cent of those considered fat. Column b shows the number of children found in each channel in 1947, column c, the number observed in 1948-1949. As will be noticed, there are 117 children listed for 1947 and 132 children for 1948-1949; therefore, if the pattern of the distribution had not changed, the figures expected for 1948-1949 are found by multiplying each row in b by 132/117; the result is listed under d (for example, $25 \times 132/117 = 28.20$). Here again a chi-square [6] test is used to compare the observed and the expected distribution shown under c and d. By subtracting in each row the expected number from the observed number, column e is obtained. Squaring the values in column e gives column f; dividing the values in column f by the appropriate expected

5. A very useful chart of the chi-square distribution has been designed by Prof. C. I. Bliss. Copies are distributed, free of charge, by the Department of Pharmacology of Yale University.

6. An explanation of the steps to follow can be found in any text on statistics.

figure, *d*, yields the values in column *g*, the sum of which is the chi-square. Since there are two distributions (columns) to be compared and six channels (rows), the number of degrees of freedom is five. For five degrees of freedom a chi-square of 20.52 would indicate a probability of $p = 0.001$ of such an occurrence by chance, and our figure (53.07) is still higher. We may therefore confidently say that the children are by far leaner in 1948-1949 than they were in 1947.

Combining the two results, it may be said that the children were better developed in 1948-1949 than they were in 1947, but this improvement in standing (as judged from the decrease in number of those falling below the age standard) did not reach the level of significance ($p = 0.07$). In 1948-1949, however, a highly significant ($p =$ less than 0.001) displacement of the children toward the lean side was brought about.

COMMENT

The result obtained from the number of children falling below their appropriate age standard and the result obtained from the channel distribution seem to be at variance; but this is not the case. For the children, very poorly fed during the siege, obtained much more food after the siege than probably ever before. When a poor diet improves, height is usually gained earlier or faster than weight.[7] Therefore, as Campbell and Weir [7] have pointed out, a single nutritional index, like Tuxford's index, may give during this stage the false impression of a greater degree of undernourishment. These defects of Tuxford's index are due to the failure of the simple height-weight ratio to make full allowance for the normal change in development. This pitfall seems to be avoided in the present method.

SUMMARY

A test for trend in the bodily development of school children is suggested, employing height-weight-age charts previously described. As the height-weight-age relation and the height-weight ratio are tested separately, trends can be more easily followed than with use of a single compound formula for height-weight-age, which may lead to erroneous results.

7. Campbell, F. W., and Weir, J. B. de V.: Tuxford's Index of Nutrition: A Convenient Nomogram, Brit. J. Nutrition **2**:120-122 (Oct.) 1948.

"TWEEN 20" AND FECAL FAT IN PREMATURE INFANTS

A Preliminary Study

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A PREMATURE infant is beset with many problems in his effort to carry himself through the critical early days of his life. Among his many difficulties are digestive disturbances and a low tolerance for ingested fat. It has been proved by several investigators that premature infants generally absorb less dietary fat than do full term infants and accordingly produce more fecal fat. Gordon and McNamara,[1] in a series of 48 observations on premature infants, found that 90 per cent of the infants presented fecal fat values of over 69 per cent when fed on cow's milk formulas. Six normal full term infants, used as controls, showed fecal fat values ranging from 27 to 65 per cent, with an average of 40 to 50 per cent. These values were found to be highly individualistic and variable, however, in both groups of infants. In addition, Gordon and McNamara observed that skimmed milk formulas in premature infants yielded lower fecal fat values, approaching the same values as those observed for full term babies receiving whole milk formulas. They therefore advocated the feeding of low fat diets to premature babies.

Holt, Tidwell and others[2] likewise demonstrated the fact that absorption of fat in premature infants is defective. They also concluded

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This investigation was made possible through a Fellowship Grant from the Division of Research Grants and Fellowships of the United States Public Health Service, Federal Security Agency.

1. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: I. Effect On Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child. **62**:328 (Aug.) 1941.

2. Holt, L. E., Jr.; Tidwell, H. C.; Kirk, C. N.; Cross, O. M., and Neale, S.: Studies in Fat Metabolism: I. Fat Absorption in Normal Infants, J. Pediat. **6**:427 (April) 1935. Tidwell, H. C.; Holt, L. E., Jr.; Farrow, H. H., and Neale, S.: Studies in Fat Metabolism: II. Fat Absorption in Premature Infants and Twins, ibid. **6**:481 (April) 1935.

that certain vegetable fats when incorporated into formulas produced better absorption and lower fecal values than did milk fat. Therefore the use of olive oil-milk formulas was advocated.

We decided to study further the feeding of premature infants in relation to lipid absorption by directing our attention to the problem of fat emulsification, which is but one of the many factors significant in this phase of digestion. Some other important factors involved in fat absorption are (1) nature of the fat (presence of more than one bond in the fatty acid chain); (2) presence of the digestive juices, enzymes and bile salts; (3) patency of the lacteals; (4) motility of the intestine; (5) integrity of the intestinal mucosa, and (6) integrity of the physiologic mechanisms involved in the transportation of fats.

Our attention was turned recently to the use of "wetting agents" as aids in the emulsification of fats. These substances, by trade name the "tweens," [3] have been used industrially for the distribution of fatty substances in lipid or aqueous mediums, by virtue of their action on surface tension, in the preparation of flavors, perfumes and other substances. They are surface-acting agents, consisting of partial esters of long chain fatty acids with polyoxyalkylene derivatives of the hexitol anhydride (as sorbitan or mannitol). In 1945, Dubos [4] used "tween 60" for the dispersion of the lipid-encapsulated tubercle bacilli in aqueous culture mediums. Recently, reports [5] have appeared in the literature regarding the effect of "tweens" on the absorption of fat in the steatorrheas of older children and adults. We decided to study the effects of "tween 20" (polyoxyethylene derivative of sorbitan monolaurate) on the fat absorption in premature infants. This drug has been subjected to 10 years of toxicologic research on animals by Krantz,[3] who found it to be nontoxic.

TECHNIC OF PROCEDURE

The observations were carried on over a period of 337 days and involved 13 premature babies and two older infants with steatorrhea. Twenty-four hour stools were collected every four days from each child. All the infants received half-skimmed milk formulas (dryco®) fortified with dextri-maltose® no. 1 (with 2 per cent added sodium chloride). The formulas contained 1.5 per cent fat. This feeding regimen was routine in the newborn service prior to this study. According

3. Feeding Test Studies on Mannitol Sorbitol and Some of Their Fatty Acid Reaction Products: Atlas Powder Company, Wilmington, Del.

4. Dubos, R. J.: Rapid and Submerged Growth of Mycobacteria in Liquid Media, Proc. Soc. Exper. Biol. & Med. **48**:361 (April) 1945.

5. Jones, C. M.; Culver, P. J.; Drumney, G. D., and Ryan, B. A.: Modification of Fat Absorption in the Digestive Tract, Ann. Int. Med. **29**:1 (July) 1948. May, C. D.; Lowe, C. U., and Slenberg, A.: The Absorption of Orally Administered Emulsified Lipid in Normal Children with Steatorrhea, J. Clin. Investigation **27**: 226 (March) 1948.

to previous experiments,[6] a maximum of 95 per cent retention of ingested milk was arbitrarily assumed for each child. Prior to the study, eight premature infants were given 0.5 Gm. doses of charcoal as an intestinal marker. It was found that the average child required 3½ to 4 days to eliminate this agent completely. It was for this reason that a four day interval for the collection of stools was used.

The stools were collected on disposable diapers, the soiled portions of which were placed in sputum boxes. The external genitalia of the infants were swathed in cotton to prevent mixing of urine and feces. Only water or alcohol was used to cleanse the buttocks.

The stools were carefully scraped from the soiled napkins, placed in Petri dishes and dehydrated at 60 F. in a drying oven for three days. The material was then weighed, and fat extractions were done on 0.5 Gm. aliquots according to the micromethod suggested by Sobel.[7]

As far as possible (depending on the weight of the infant, his condition and, therefore, the length of his stay in the hospital) stools were collected over a period of one month. Attempts were made to collect at least two stool specimens prior to the administration of "tween 20" and at least two after its discontinuation.

"Tween 20" was used in a 20 per cent weight/volume strength, each 1 cc. containing 200 mg. Since the dosage of this emulsifying agent had not been established for clinical use, it was thought wise, especially for premature infants, to begin with small amounts. Accordingly, the first infants received initial doses of 0.12 ml. (2 minims) four times daily, and the dose was gradually increased until late in the study 1 cc. was given four time daily. The measured amounts of the drug was administered orally from a medicine dropper.

RESULTS OF STUDY

The results of the study are shown in the table. It was noted that generally these infants presented low fecal fat values with or without the emulsifier. A total of 90 stool specimens were examined. The lowest fat value of the prematures at any time during the period was 11 per cent (infant 27) and the highest 57 per cent (infant 17). The mean fecal fat value was 27.3 per cent prior to administration of "tween 20," 32.7 per cent during administration and 25.2 per cent after its discontinuation. There was an element of constancy for all the babies; those tending to have lower fecal fat values continued having them, and those having slightly higher values continued having them. There was no consistent diminution in stool fat with the addition of "tween 20." The drug had no laxative effect. The average number of bowel movements by each baby before and during the therapy was 2.4 and 2.3 daily respectively. There was no obvious anorexia and no vomiting or diarrhea, with one possible exception, in one of the full term infants (infant 35). In infant 42, a premature, diarrhea developed during the

6. Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and in Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940.

7. Sobel, A. E.: Quantitative Micro-Chemistry in Clinical Laboratories, Indust. & Engin. Chem. (Analyt. Ed.) **17**:242, 1945.

administration of "tween 20," but reinstitution of its use after cessation of the diarrhea failed to produce loose stools. Weight gain was progressive in all the infants except infant 42.

Six of the 13 premature infants failed to show consistent increase in fat retention in response to "tween 20" (infants 17, 29, 33, 34, 39 and

The Effect of "Tween 20" on Fecal Fat in Thirteen Premature Infants and Two Full Term Infants with Steatorrhea*

	Weight		Observation No.	Study Period, Days	Per Cent of Fat Before Administration of "Tween 20"	Per Cent of Fat During Use of "Tween 20"†	Per Cent of Fat After Use of "Tween 20"
	Lb.	Oz.					
Premature infants							
D. T.	2	7	17	53	Fecal, 17, 25	29 (2), 30 (2), 36 (2), 30 (2), 26 (2), 48 (2), 47 (2), 53 (2), 57 (2), 54 (2), 52 (2), 47 (2), 54 (2)	.....
					Retained, 77, 84	71.2, 72, 80.3, 81.8, 77.7, 62, 60, 51, 86.3, 60, 53, 61.3, 79.2	.....
C. P.	3	0	29	41	Fecal, 24, 35, 41	41 (2), 35 (3), 37 (3), 35 (4), 41 (4), 37 (4), 25 (4)	.....
					Retained, 88.6, 75, 73	55, 84.7, 92.5, 85, 63, 64, 80	.....
H. F.	3	8	13	34	Fecal, 34, 29, 24, 11, 42 Retained, 82.6, 77.3, 93.3, 94.1, 43	55 (2), 26 (2), 20 (3) 81, 89.2, 96.2	.....
E. R.	4	14¼	34	18	Fecal, 17, 25 Retained, 77, 83	17 (3) 61	16, 19 95, 97.2
A. B.	3	12	27	25	Fecal, 13, 30, 40, 23 Retained, 96.5, 83, 85.9, 87	22 (3), 11 (3) 87, 98.1	.....
M. B.	3	9	33	34	Fecal, 38, 22, 20 Retained, 62.6, 97.5, 68.9	25 (3), 36 (4), 37 (4), 47 (10) 76.5, 86.5, 63, 87	.....
A. J.	4	13	38	22	Fecal, 20, 20 Retained, 74, 88.5	20 (4), 17 (4) 91.1, 87.3	23, 23 63.7, 89.3
W. R.	4	13	39	22	Fecal, 22, 30 Retained, 89, 78.7	26 (4), 34 (4) 95.1, 79	33, 27 80, 91
A. W.	4	1¼	40	22	Fecal, 32, 25 Retained, 90, 90.6	27 (4), 15 (4), 22 (4), 26 (4) 91.5, 99, 91.4, 88	.....
L. S.	4	11	41	14	Fecal, 31, 27 Retained, 68, 81	36 (10), 35 (10) 74, 75	.....
M. S. #1	4	12	43	13	Fecal, 24, 16 Retained, 65, 98	16 (10), 19 (10), 29 (10) 97.8, 93.5, 82	.....
M. N.	3	12¾	42	25	Fecal, 36, 39 Retained, 80.6, 65.6	30 (10), 27 (10), 32 (10), 31 (10) 81.5, 90.5, 85.7, 77.5	36 33
M. S. #2	4	9½	44	13	Fecal, 27, 28 Retained, 76, 78	29 (15), 28 (15) 89.6, 90	.....
Full term infants							
J. D.	10	14	37	31	Feca', 68, 55	65 (4), 58 (4), 60 (4), 79 (15), 78 (15), 53 (10)	.....
B. P.	7	4	36	27	Fecal, 52, 49	65 (4), 60 (4)	

* Stools were collected at four day intervals.
† Figures in parentheses indicate the dose in minims.

41). Of the seven others, only infant 44 showed an increase above 10 per cent. This child was receiving the maximum dose of the drug used in this series.

The two older children with steatorrhea showed no decrease in stool fat while receiving "tween 20." For infant 36 a diagnosis of intrahepatic biliary obstruction was made at operation. This baby later died, and the diagnosis was confirmed at autopsy. His stool fat content rose progressively to 79 per cent. Infant 35 had obstructive jaundice, probably

on the basis of inspissated bile, and gradually improved with supportive therapy. During the administration of "tween 20" there was no decrease in fecal fat in this infant. Loose stools of undetermined origin developed while this baby was taking "tween." We do not have data on the exact intake of fat of these two infants.

COMMENT

It appears that "tween 20" in the dosages used was not any more effective in reducing stool fat than is a low fat diet per se. The low fecal fat values in this study as well as the inconsistent fat retention may be the result of several factors: low dietary fat, inefficiency of the particular emulsifier employed and inconspicuous technical difficulties relative to dietary intake, regurgitation and stool collection. The results pose three questions:

1. Is fecal fat a true index of fat absorption?

2. Are solubility and particle size of the fat molecules real factors in lipid absorption?

3. Was the drug employed in an adequate dosage?

In regard to the question of fecal fat as an index of fat absorption, it is thought that in normal persons fecal fat is constant regardless of diet.[8] In these instances fecal fat is essentially endogenous. However, in abnormal subjects fecal fat analysis may reflect faulty absorption of lipids, as is dramatically illustrated in the steatorrhea accompanying cystic fibrosis of the pancreas, celiac syndrome, obstructive jaundice and similar conditions. The same reasoning can be applied to the premature infant, who is physiologically inadequate. It would prove interesting to place premature infants on normal fat or high fat diets and then to study the effects of "tween 20." The fact that the majority of the premature infants employed in this study weighed more than 3½ pounds (1,525 Gm.) may also account in part for the low fat values. The stool fat tends to decline with increasing weight and maturity of the infant.[2]

In regard to particle size, Holt, Tidwell and others[2] stated the belief that this factor has no bearing on fat absorption. Our findings might well substantiate their claim, since none of the infants showed decreased fecal fat while taking the emulsifier.

The optimum dosage of "tween 20" for premature infants is yet to be established. In future studies of this type it would be of interest to employ larger doses, since the drug is apparently nontoxic.

In retrospect, since the bowel habits of premature infants are so capricious, perhaps it would have been better to collect 24-hour specimens

8. Kleiner, I. S.: Human Biochemistry, ed. 2, St. Louis, C. V. Mosby Company, 1948, pp. 219-220.

for three or more consecutive days. Such a sustained and continuous collection might have presented a truer picture of intestinal absorption and the effects of "tween 20."

SUMMARY AND CONCLUSIONS

The effect of "tween 20," a new wetting agent, on fecal fat was studied in 13 premature infants and in two full term infants with steatorrhea. Fecal fat content was analyzed before, during and after the administration of the emulsifier.

Six of the 13 premature infants failed to show increase in fat retention during the administration of the drug. Seven of the infants exhibited a slight increase in fat retention while taking "tween 20."

From this study the following conclusions were made:

1. "Tween 20" was no more effective in reducing fecal fat than was skim milk alone.

2. The drug had no apparent effect on fecal fat content of two full term infants with steatorrhea.

3. "Tween 20" in the dosages used was apparently nontoxic.

This represents a preliminary study. Further investigation to determine the effects of "tween 20" on prematures with average or high fat diets as well as an employment of the drug in larger doses would be of interest.

The "tween 20" employed in this work was supplied by Endo Products, Inc., Richmond Hill, N. Y.

The nurses in the newborn service cooperated in the collection of specimens under the supervision of Mrs. Lucille McElvane.

Dr. Albert E. Sobel, Jewish Hospital, Brooklyn, gave advice and suggestions.

FACTORS INFLUENCING RETENTION OF NITROGEN AND CALCIUM IN PERIOD OF GROWTH

VIII. Influence of Rest and Activity

JOSEPH A. JOHNSTON, M.D.
DETROIT

REST has been accepted until recent years as a principle of treatment of many chronic illnesses, notably tuberculosis and rheumatic heart disease. To the extent that the retentions of nitrogen and calcium can be taken as paralleling healing (and in tuberculosis it is felt that healing correlates with adequate storage of nitrogen and calcium in the growth period [1]), the known depressing effects of inactivity on their retention would make the employment of this measure questionable unless it could be shown that other desirable effects offset this disadvantage. Even then, however, thought should be given to the possibility of securing the worth while effects of activity without sacrificing any gains achieved by rest.

In a recent symposium on this subject, internist, surgeon, orthopedist, psychiatrist and cardiologist joined in questioning the value and indicating the harmful effects of prolonged bed rest on the basis of clinical observations. Harrison,[2] in addition, cited experiments in which myocardial injury was induced in rats and comparison made of mortality between those restricted and those permitted activity, the death rate being greater in the former. He concluded:

> There is no proof that rest in bed carried out for many weeks after symptoms have disappeared is of value in the physical management of the patient with congestive failure, angina pectoris or myocardial infarction.
>
> Persons with congestive failure should be allowed out of bed for several hours a day, as soon as severe dyspnea has subsided.
>
> In all patients with the severe forms of heart disease activity should be kept below the symptomatic threshold, i. e. should be less than that amount which induces dyspnea or pain.

From the Department of Pediatrics, Henry Ford Hospital.

1. Johnston, J. A.: On the Possible Relation of Nutrition to the Development and Course of Tuberculosis, in the Saranac Laboratory Symposium on Tuberculosis in Industry, 1941, New York, National Tuberculosis Association, 1942.

2. Harrison, T. R.: Abuse of Rest as a Therapeutic Measure for Patients with Cardiovascular Disease. J. A. M. A. **125**:1075 (Aug. 19) 1944.

In the discussion of this paper, Allen stated that there is no good evidence that recurrence of rheumatic fever results from activity. Dock's [3] concluding statement in this contribution to the symposium is worth repeating: "The physician must always consider complete bed rest as a highly unphysiologic and definitely hazardous form of therapy, to be ordered only for specific indications and discontinued as early as possible."

In tuberculosis, the relative merits of rest and graded activity were reviewed by Pratt.[4] While making a good case for the former, he spoke of four months as an average for complete inactivity. In our studies on tuberculosis in the adolescent, even in the absence of fever or elevation of the pulse rate, rest in the early months of treatment is accompanied with steadily mounting retentions, the basal metabolic rate tending either to fall or to remain about normal.[1] Beyond this point, storage declines with continuation of the bed rest regimen and improves with moderate activity. This seemingly contradictory finding at two stages of the disease process, both without fever or pulse elevation, may be accounted for by the fact that any tendency toward diminished retentions due to bed rest would be offset by a stronger tendency in the opposite direction to replenish depleted stores, and when this has been accomplished subsequent balances may be expected to show the decline incidental to inactivity. Browne [5] and his group, in demonstrating a straight line correlation between intake and retention in debilitated patients, showed that storage was twice as great on a given intake for the debilitated patient as for the normal control.

The metabolic changes induced by rest were classically recorded by Cuthbertson [6] on eight subjects with noninfectious orthopedic conditions during periods of rest in bed ranging from 11 to 48 days. There were noted losses of nitrogen, sulfur, phosphorus and calcium. The sulfur-nitrogen ratio suggested a sulfur-rich source of the excreted material, presumably for the most part muscle. In the studies of Allison and Brooks [7] on the atrophy of disuse, there was noted a frank diminution in the amount of mineral, but the percentage per unit of bone was

3. Dock, W.: The Evil Sequelae of Complete Bed Rest, J. A. M. A. **125**: 1083 (Aug.) 1944.

4. Pratt, J. H.: Rest Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **50**:185, 1944.

5. Browne, J. S. L.; Schenker, V., and Venning, E. H.: Feeding During Convalescence, in Reifenstein, E. C., and Adams, H.: Conference on Metabolic Aspects of Convalescence: Transactions of the Thirteenth Meeting, New York, Josiah Macy, Jr. Foundation, 1947.

6. Cuthbertson, D. P.: The Influence of Prolonged Muscular Rest on Metabolism, Biochem. J. **23**:1328, 1929.

7. Allison, N., and Brooks, B.: Bone Atrophy, Surg., Gynec. & Obst. **33**:250. 1921.

unchanged. Albright's [8] explanation of bony disuse atrophy is that, since the normal stimulus to the osteoblasts is stress and strain, immobilization will lead to decreased osteoblastic activity and, resorption continuing, osteoporosis will result.

A series of studies from the metabolic standpoint was given impetus by the recent war and is recorded in the "Conferences on Metabolic Aspects of Convalescence." Keys [9] reported that at bed rest four normal men who had been in nitrogen equilibrium in their foreperiods showed steadily increasing negative balances for three weeks, with losses totaling as high as 366 Gm. of protein. In the first week out of bed, all balances became positive. The potassium balance was uniformly negative. Deitrick, Whedon and Shorr [10] described marked increases in the excretion of nitrogen, calcium and phosphorus of subjects in casts. There was also measured a progressive failure of circulatory reflexes essential for the maintenance of adequate circulation in the erect position and a progressive generalized weakness and easy fatigability which seemed out of proportion to that which could be recorded by any of the tests. With the oscillating bed, two of three subjects showed a 50 per cent reduction in their losses of nitrogen and two showed a similar reduction in calcium lost.

All physiological functions have an optimal point, above and below which efficiency is reduced. Work increases nitrogen output, though not to an extent that parallels the increased energy expenditure. Carbohydrate is accepted as the chief source of the increased oxygen consumption. In the study of Cathcart and Burnett [11] the mere addition of meat extractives practically obliterated the increased urinary nitrogen that accompanied extra work.

The children here to be described were hospitalized for a variety of reasons. "Rest" as used here is a relative term, implying merely confinement to bed, which in a pediatric ward carries with it none of the connotation that it does in an adult ward or for persons in a body cast. In one case a knee cast was used. "Exercise" includes freedom of the

8. Albright, F., and Reifenstein, E. C. Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948.

9. Keys, A.: Effect of Bed Rest on Nitrogen Balance of Normal Individuals, in the Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing: Transactions of the Seventh Meeting, New York, Josiah Macy, Jr. Foundation, 1944.

10. Deitrick, J. E.; Whedon, G. D., and Shorr, E.: Effects of Immobilization upon Various Metabolic and Physiologic Functions of Normal Men. Am. J. Med. **4**:3, 1948.

11. Cathcart, E. P., and Burnett, W. A.: The Influence of Muscle Work on Metabolism in Varying Conditions of Diet, Proc. Roy. Soc., London **99**:405, 1925-1926.

ward and walking about a block to school in another building, except where it was more specifically prescribed with a single bicycle wheel mounted on a platform and equipped with foot straps to permit its being pedaled while the child continued in the horizontal position. Children who have been at rest for months will show fatigue after pedaling this for about nine minutes. We are impressed with the very small amounts of exercise (e. g., three minutes twice a day) capable of improving retention and with the small margin that separates this anabolic effect from the catabolic effect noted when the exercise produces fatigue.

This device was chosen as a means of providing exercise because it still made possible the horizontal position which Dock feels should be maintained by a patient with a tuberculous lesion of an upper lobe. While "bed rest" as used here is far from the physiologic situation created by Deitrick,[11] it does make possible an observation on the situation usually obtaining in a children's ward where body casts are not being used.

METHODS

The methods used were described in the first two papers of this series.[12] In brief, six rotating diets are used and a pooled sample consisting of one sixth of each day's diet is analyzed for calcium and nitrogen. A minimum of 18 days is felt essential for significant results in a study of calcium. Significant changes in nitrogen will be evident in shorter periods, and in the case of S. O'N. (case 4) the plotting was broken down into three-day periods.

OBSERVATIONS

Case 1.—Robert C., a 7 year old boy, was admitted to the hospital on Feb. 6, 1945 with tuberculous cervical adenitis which had been present eight months. After two months of bed rest he was allowed to go to school one session a day in a wheel chair. His temperature reached 100 F. daily.

The metabolic observation was made while his activity was continued for 18 days, after which he returned to bed rest for 54 days, and a final 24-day observation was obtained with resumed activity. Bed rest was followed by a definite fall in the retention of both calcium and nitrogen, the fecal losses accounting for most of this in the case of calcium, though the urine excretion did rise also; urinary excretion accounted for all the increased nitrogen loss.

Case 2.—Charles J., born March 18, 1937, was found to have a tuberculous knee joint at 2 years of age. He was placed in constantly renewed casts for four years. For a month preceding the study the cast had been exchanged for braces and he had been active in the ward. He was put at strict bed rest again for the first 36 days of the study. On March 18, 1945 he started to school in another building twice a day but wore a bed cast at night and during rest periods. Use of the cast was discontinued altogether on March 29. The sedimentation rate was normal. The chest was normal. The roentgenogram was interpreted as showing considerable osteoporosis of the right knee, no narrowing of joint space and no

12. Johnston, J. A., and Maroney, J. W.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: I. Effect of Thyroid on Nitrogen Retention, Am. J. Dis. Child. **58**:965 (Nov.) 1939; II. Effect of Thyroid on Calcium Retention, ibid. **58**:1188 (Dec.) 1939.

destruction along the articular surface. There was one area of destruction in the medial portion of the epiphysis; it appeared old.

There was a fall in the second 18 day period of retention of nitrogen from 3.20 to 2.27 Gm. a day and a return to 2.67 Gm. a day with activity; calcium retention

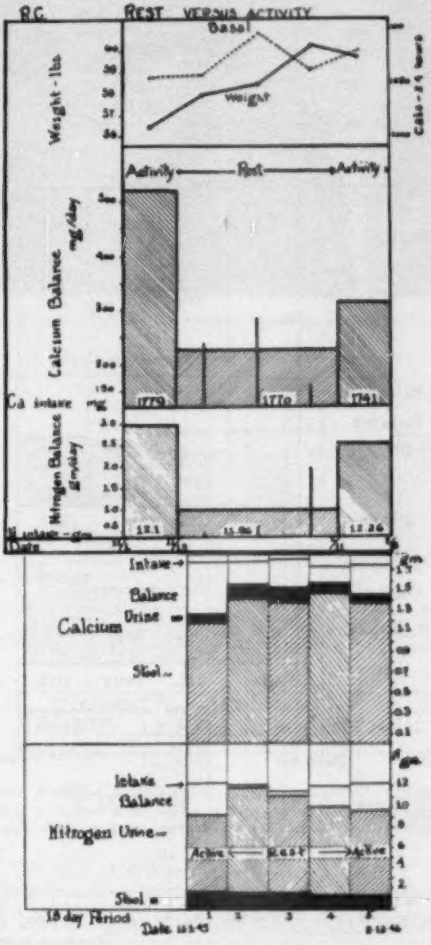

Fig. 1 (case 1).—Nitrogen and calcium balances during the last 18-day period of bed rest and the final 18-day period of observation, when the patient resumed activity. It is evident that the diminished retention of nitrogen was due to greater urinary output but the calcium losses were largely fecal, though there was a rise also in the urinary output of calcium.

TABLE 1.—*Balance Observation in Case 1*

Observation Period	Dates	Nitrogen, Gm./Day: Average Urine	Average Stool	Intake	Balance	Calcium, Gm./Day: Average Urine	Average Stool	Intake	Balance	Basal Calories, 24 Hr.	B. M. R.* B.	W.	Weight Lb.	Kg.	Ht. In.	Diet Calories	Comment
1	11/ 1-11/18	7.68	1.55	12.11	+2.95	0.008	1.186	1.779	+0.585	1,055	—10	—3	56½	25.6	49	1,900	Activity
2	11/19-12/ 6	10.06	1.56	12.09	+0.45	0.140	1.410	1.789	+0.239	1,058	—10	—3	58	26.3	..	.....	Bed rest
3	12/ 7-12/24	9.39	1.54	11.51	+0.58	0.131	1.379	1.797	+0.287	1,091	— 7	—1	58½	26.5	..	.....	Bed rest
4	12/25-1 /11	8.64	1.49	11.99	+1.86	0.101	1.403	1.795	+0.161	1,093	— 9	—4	60¼	27.3	..	.....	Bed rest
5	1 /20-2 /12	8.13	1.46	12.30	+2.71	0.092	1.360	1.739	+0.287	1,104	—14	0	60	27.2	..	.....	Activity

* In this and succeeding tables, B indicates the basal metabolic rate referred to in the Boothby-Sandiford table; W, the prediction made with the Wetzel grid.

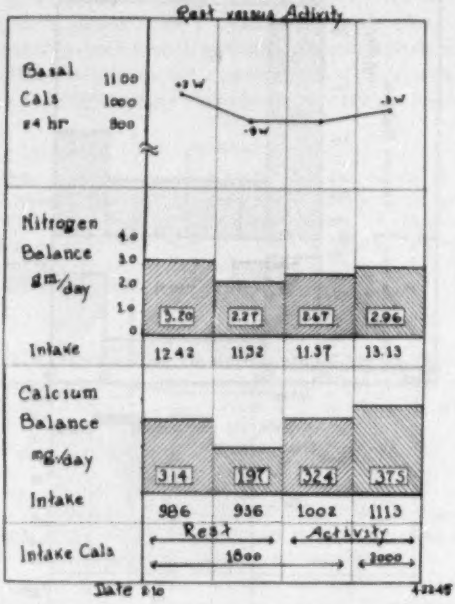

Fig. 2 (case 2).—Nitrogen and calcium balances of a patient with a tuberculous knee. In the second 18-day period of rest following a month of activity, retentions fell 30 per cent; they rose again as the patient began to walk about the ward.

TABLE 2.—*Balance Observations in Case 2*

18 Day Period No.	Dates	Nitrogen, Gm./Day: Average Urine	Average Stool	Intake	Balance	Calcium, Gm./Day: Average Urine	Average Stool	Intake	Balance	Basal Calories	B. M. R. B.	W.	Weight Lb.	Kg.	Ht. In.	Comment
Rest 1	2/10-2/27	8.36	0.86	12.42	+3.20	0.025	0.646	0.986	+0.314	1,055	— 5	+2	50	22.6	48½	1,800 calory diet
Rest 2	2/28-3/17	8.83	0.92	11.52	+2.27	0.037	0.702	0.936	+0.197	959	—16	—9	51	23.0	..	....
Act. 3	3/18-4/4	7.59	1.11	11.37	+2.67	0.016	0.692	1.002	+0.324	942	—17	—7	48½	21.8	49½	....
Act. 4	4/ 5-4/22	8.97	1.30	13.13	+2.96	0.012	0.726	1.113	+0.375	981	—12	—3	50	22.6	..	2,000 calory diet

Fig. 3 (case 2).—Marked osteoporosis on February 17.

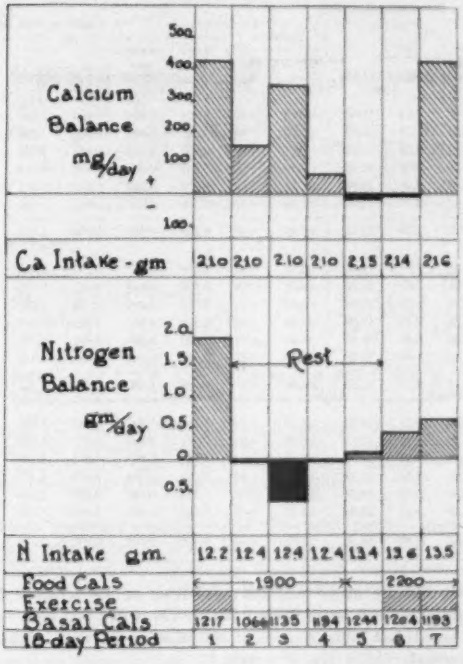

Fig. 4 (case 3).—Period 1 is the last 18 days of activity. During the four periods the patient was confined to bed but restraints were not used. During the next 36 days the patient pedaled the bed bicycle for nine minutes twice a day.

fell from 314 mg. to 197 mg. a day and returned to 324 mg. per day. In a fourth period there was a further rise to 2.96 Gm. a day of nitrogen and 375 mg. a

TABLE 3.—*Balance Observation in Case 3*

18 Day Period No.	Dates	Nitrogen, Gm./Day: Average Urine	Average Stool	Intake	Balance	Calcium, Gm./Day: Average Urine	Average Stool	Intake	Balance	Basal Calories, 24 Hr.	B. M. R. B.	B. M. R. W.	Weight Lb.	Weight Kg.	Ht. In.	Diet Calories	Comment
1	8/18- 9/ 4	9.25	1.09	12.22	+1.88	0.122	1.557	2.105	+0.425	1,217	−3	+5	74	33.6	55	1,900	Exercise Dicalcium phosphate, 0.600 Gm.
2	9/ 5- 9/23	11.25	1.19	12.40	−0.04	0.248	1.697	2.105	+0.160	1,066	−14	−8	74	33.6	..	.....	Rest
3	9/23-10/10	11.98	1.08	12.39	−0.67	0.211	1.548	2.105	−0.346	1,135	−9	−2	74½	33.7	..	.....	Rest
4	10/11-10/28	11.14	1.28	12.39	−0.06	0.151	1.869	2.105	+0.085	1,194	−7	+2	75½	34.2	55¼	2,200	Rest
5	10/29-11/15	11.71	1.52	13.40	+0.17	0.126	2.046	2.105	−0.022	1,244	−2	+5	76½	34.7	..	.....	Rest
6	11/16-12/ 5	11.41	1.79	13.60	+0.40	0.127	2.043	2.157	−0.013	1,304	−6	+3	79	35.8	..	.....	Exercise 9 min. in bed
7	12/ 4-12/21	11.92	1.06	13.51	+0.62	0.109	1.618	2.157	+0.430	1,196	−9	±0	80¼	36.4	..	.....	....

TABLE 4.—*Balance Observations in Case 4*

8 Day Period No.	Dates	Nitrogen, Gm./Day: Average Urine	Average Stool	Output	Intake	Balance: Gm./Day	Balance: Mg./Kg.	Calcium, Gm./Day: Average Urine	Average Stool	Output	Intake	Balance: Gm./Day	Balance: Mg./Kg.	Basal Calories, 24 Hr.
Rest														
1	11/ 8-11/10	6.50	0.68	7.18	11.00	+3.82	+87	0.028	0.636	0.664	1.045	+0.381	8.7	.....
2	11/11-11/13	8.28	0.96	9.24	11.02	+1.78	+40	0.027	0.948	0.975	1.044	+0.069	1.4	.....
3	11/14-11/16	7.40	1.10	8.50	11.07	+2.57	+58	0.035	0.892	0.927	1.005	+0.078	1.6	.....
4	11/17-11/19	7.77	0.78	8.55	10.95	+2.40	+55	0.049	0.619	0.668	1.012	+0.344	7.9	.....
5	11/20-11/22	8.38	0.96	9.36	10.88	+1.52	+35	0.052	0.597	0.649	0.971	+0.322	7.4	.....
6	11/23-11/25	8.61	1.01	9.62	11.94	+2.32	+53	0.104	0.711	0.815	1.065	+0.250	5.0	.....
	Average	7.82	0.92	8.74	11.14	+2.40	+55	0.049	0.734	0.783	1.019	+0.236	5.3	1,163
Exercise														
7	11/26-11/28	8.47	1.31	9.78	12.46	+2.68	+61	0.086	0.885	0.971	1.096	+0.125	2.8	.....
8	11/29-12/ 1	5.98	0.65	6.63	12.22	+5.59	+129	0.070	0.440	0.510	1.132	+0.622	14.1	.....
9	12/ 2-12/ 4	7.35	0.93	8.28	12.08	+3.80	+87	0.076	0.685	0.761	1.205	+0.444	10.2	.....
10	12/ 5-12/ 7	8.46	1.33	9.79	12.08	+2.29	+52	0.111	0.921	1.032	1.205	+0.173	3.9	.....
11	12/ 8-12/10	7.89	0.96	8.85	12.27	+3.42	+77	0.090	0.608	0.698	1.135	+0.437	9.8	.....
12	12/11-12/13	10.16	1.56	11.69	12.27	+0.58	+13	0.081	0.542	0.623	1.135	+0.511	11.5	.....
	Average	8.05	1.12	9.17	12.25	+3.06	+70	0.086	0.680	0.766	1.151	+0.385	8.7	1,176
Exercise														
13	12/14-12/16	8.77	1.34	10.11	12.23	+2.12	+48	0.105	1.043	1.148	1.096	−0.052	1.2	.....
14	12/17-12/19	11.12	1.10	12.22	12.23	+0.01	+02	0.142	0.815	0.957	1.096	+0.139	3.1	.....
15	12/20-12/22	11.06	1.06	12.09	12.32	+0.43	+10	0.112	0.863	0.975	1.107	+0.132	3.0	.....
16	12/23-12/25	9.15	1.09	10.24	12.44	+2.20	+49	0.084	0.791	0.875	1.126	+0.251	5.4	.....
17	12/26-12/28	9.91	0.80	10.80	12.39	+1.49	+33	0.115	0.694	0.809	1.165	+0.356	8.0	.....
18	12/29-12/31	8.72	1.18	9.90	12.02	+2.73	+61	0.130	0.894	1.000	1.152	+0.122	2.7	.....
	Average	9.78	1.11	10.89	12.30	+1.50	+34	0.116	0.850	0.966	1.124	+0.158	3.9	1,210

day of calcium, but the intake was increased from an 1,800 calory diet to 2,000 calories. Basal calories dropped from 1,055 to 939 a day and rose to 981 a day. It should be noted that with the rise of retention in the third period there was a loss of 2¼ pounds (1.02) Kg. of weight.

Case 3.—Phyllis, F., a Negro girl born April 1, 1940, was admitted on May 18 with cervical adenitis and a positive tuberculin reaction. Biopsy of a lymph node showed tuberculosis. She was treated with streptomycin for three months, during which time she was moderately active. Strict bed rest was enforced from September 10 until November 19. In the first 18-day period which followed rest, nitrogen fell from + 1.48 to — 0.97 Gm. a day and calcium from + 191 to — 189 mg. a day.

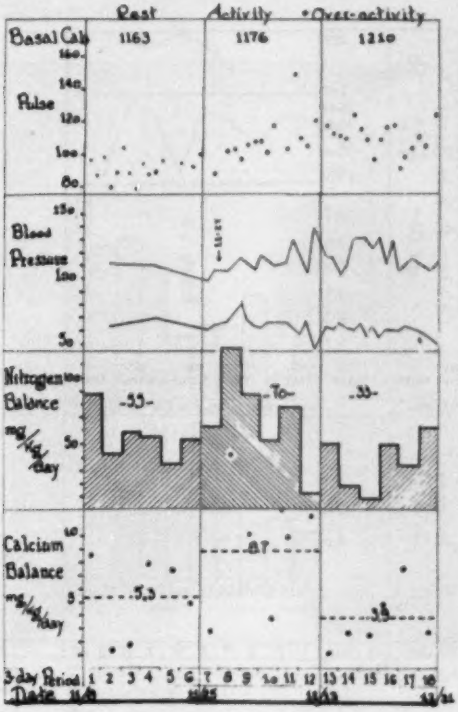

Fig. 5 (case 4).—Anabolic effects of small amounts of exercise and catabolic effects of fatiguing amounts. Peak retentions were observed with six to nine minutes of activity twice a day; fatigue occurred with amounts of more than 10 minutes. One effect of exercise was increased intakes.

The balances continued negative until the sixth period, when exercise on the bicycle was resumed up to nine minutes twice a day. The nitrogen balance immediately became positive; the calcium balance did not become positive until the next period. Increasing the intake in the fifth period did not result in a positive balance. Urinary loss of calcium doubled in the first 18-day period of rest.

Case 4.—Sally O'N., born March 26, 1924, had been placed at bed rest with a minimal tuberculous lesion on Sept. 19, 1946. When the exercise observation was begun on Oct. 3, 1947, the lesion already had receded and was scarcely visible.

She was allowed to pedal the bed bicycle from five minutes twice daily increasing to 13 minutes twice daily, at which time she showed fatigue.

In the metabolism of the adolescent there is a cyclic character to the retentions of nitrogen and calcium whose basis is not clear. It is evident before menstruation has begun, and in one child the low points occurred at intervals of about sixty days. This fact makes comparison of alternating periods of rest and activity difficult to evaluate. There are averaged ten 18-day periods (180 days) during which she was at bed rest and these are compared with five 18-day periods

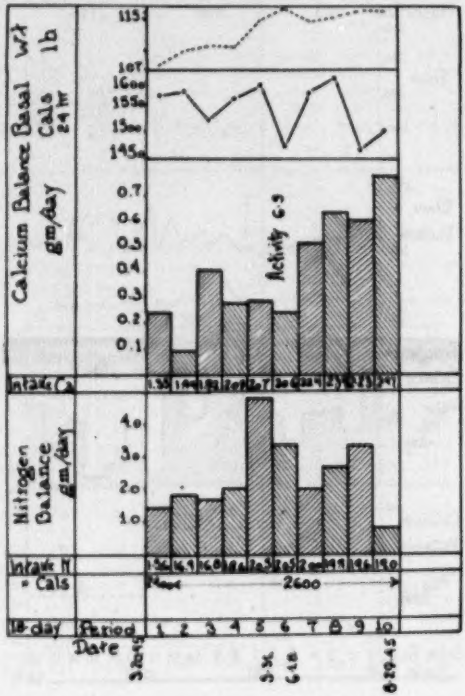

Fig. 6 (case 5).—Nitrogen and calcium balances of a 15 year old boy with reinfection tuberculosis who was allowed activity while the disease was still active.

(90 days) of exercise. The difference in nitrogen retention was slight, 2.56 Gm. a day at rest compared with 2.85 Gm. a day with exercise. The effect on calcium retention was more striking, 264 mg. a day at rest compared with 312 mg. a day with exercise.

There are here reproduced graphically only three 18-day periods, the first representing the third 18-day period of bed rest, the second and third periods during which she had exercise pedaling the one wheel bed bicycle. This she did for one minute each day, increasing by one minute a day up to 15 minutes a day. She was

obviously fatigued after about 10 minutes. This was evident in the fourth three day period, when the amount of exercise had exceeded 10 minutes, and was reflected in a rise in pulse pressure and pulse rate. It appears from the chart that slight amounts of exercise improved retention but that amounts productive of fatigue depressed them.

In a single instance of fairly extensive pulmonary tuberculosis involving the upper third of the right lung, activity was permitted while the condition was still active.

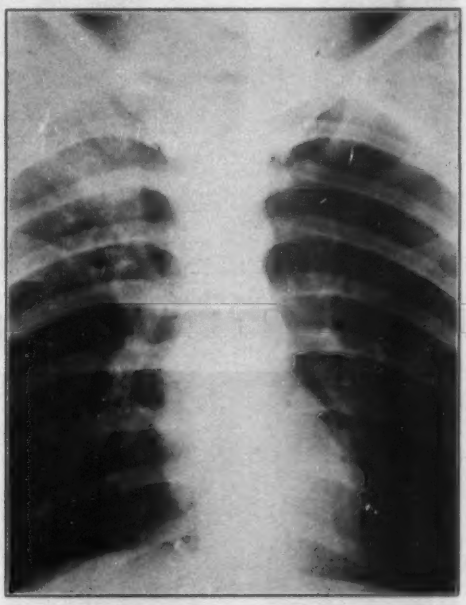

Fig. 7 (case 5).—March 18, 1945. Dense lesions in the upper half of the right lung, more marked at the level of the first interspace.

CASE 5.—M. D., born July 1, 1930, was exposed to a mother with tuberculosis and to a sister who probably died of tuberculous meningitis. Four months before admission cough with sputum and moderate dyspnea developed. He was found to react to tuberculin and to show an extensive lesion of the upper lobe of the right lung, for which he was hospitalized. The sputum did not yield tubercle bacilli. He was afebrile. The sedimentation rate was 20 mm. in one hour. The balance study was done from March 20 to Sept. 15, 1945. He was at bed rest during the first 72 days of the study, after which (June 9) he was permitted to be up for half an hour twice a day, increasing by five minutes daily up to an hour twice a day, and to attend school half a day in a wheel chair. Two sessions were allowed on July 13.

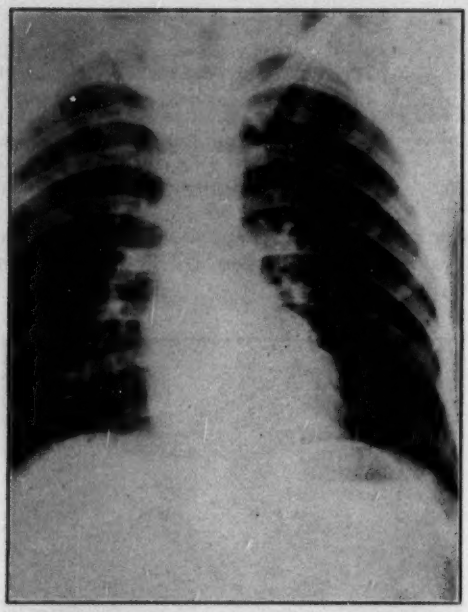

Fig. 8 (case 5).—Nov. 1, 1945. The infiltration formerly seen is less dense at the level of the first interspace and third rib and now appears productive. There is no definite cavity.

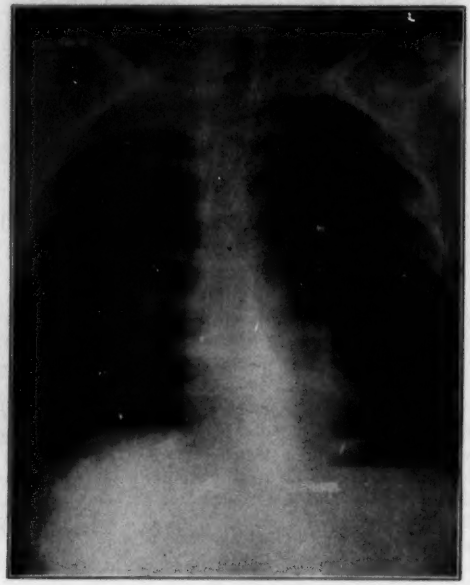

Fig. 9 (case 5).—Jan. 1, 1946. The infiltration formerly seen is definitely less extensive and more discrete.

The interpretation of the observation is complicated by the variable of an increased intake; nevertheless two points make it worth recording. Moderate activity did not result in an increase in the lesion, but, rather, some improvement occurred, and, second, an increased percentage of the intake was retained.

	Rest (72 Days)	Activity (106 Days)
Per cent of nitrogen retained	10.1	14.1
Per cent of calcium retained	14.8	22.4

It is not usual to note increasing retentions with increasing intakes after a limited point; nitrogen and calcium have "physiologic ceilings," beyond which increasing intakes are rejected in the excreta—the stool in the case of calcium and the urine in the case of nitrogen.

TABLE 5.—*Balance Observations in Case 5*

		Nitrogen, Gm./Day				Calcium, Gm./Day									
15 Day Period No.	Dates	Average Urine	Average Stool	Intake	Balance	Average Urine	Average Stool	Intake	Balance	Wt., Lb.	B. M. R. B.	B. M. R. W.	B. Q.	Basal Calories, 24 Hr.	Diet Calories	Comment
1	3/20-4/ 6	12.57	1.67	15.62	+1.38	0.164	0.944	1.354	+0.246	107½	−7	+6	.90	1,571	2,400	4/25
2	4/ 7-4/24	13.08	2.09	16.88	+1.85	0.186	1.160	1.441	+0.096	110	−7	+5	.90	1,580	2,600	Dicalcium
3	4/27-5/12	12.19	1.85	16.78	+1.74	0.170	1.340	1.918	+0.408	110½	−9	+2	.82	1,529	.....	phosphate
4	5/12-5/30	14.75	1.86	18.65	+2.04	0.208	1.602	2.088	+0.288	110½	−6	+5	.79	1,586	.....	(0.699 Gm.
5	5/31-6/17	14.12	1.49	20.52	+4.91	0.221	1.548	2.069	+0.390	114½	−12	+5	.84	1,590	.....	Ca); 5/18
6	6/18-7/ 5	15.19	1.99	20.49	+3.31	0.172	1.640	2.057	+0.245	116½	−15	−2	.75	1,473	.....	nitrogen 3.0
7	7/ 6-7/23	15.95	2.05	20.01	+2.01	0.177	1.544	2.239	+0.518	114½	−6	+5	.79	1,586	.....	Gm. as
8	7/24-8/10	15.15	2.03	19.90	+2.79	0.221	1.476	2.341	+0.644	115	−7	+6	.90	1,613	.....	amino acids
9	8/11-8/28	14.21	2.02	19.59	+3.36	0.184	1.433	2.228	+0.611	116	−15	−3	.74	1,465	.....	6/9 activity
10	8/29-9/15	16.29	1.86	19.08	+0.89	0.208	1.494	2.474	+0.778	116	−13	−1	.86	1,500	.....	

The serum proteins at the beginning and end of the observation were as follows:

	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Total, Gm./100 Cc.
5/31/45	4.86	1.55	6.44
10/31/45	4.80	2.70	7.50

It should promptly be pointed out that too great a sense of security followed this observation and when full activity with school attendance was permitted an increase in the lesion occurred, in January 1946. In this connection, it should be recalled that anabolic effects can be secured with small amounts of thyroid when the metabolism is depressed but that these quickly become catabolic on large doses [13]; so here, moderate amounts of activity may be beneficial, whereas larger amounts will be harmful.

CASE 6.—John K., born Nov. 13, 1935, gave a history of having had his first attack of rheumatic fever in 1946. He was admitted to the hospital in July 1948 with an exacerbation of symptoms and at that time showed severe cardiac damage, with mitral insufficiency and stenosis, and aortic insufficiency. He was at bed rest constantly, and metabolic observations were begun two months after admission. A second set of observations was obtained four months after admission.

During the first observation period of 54 days the sedimentation rate was never below 26 and the sleeping pulse rate was 96. Exercise consisted of pedaling

13. Johnston, J. A.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: V. Further Evidence of the Anabolic Effect of Thyroid on Calcium Metabolism, Am. J. Dis. Child. **62**:1172 (Dec.) 1941.

TABLE 6.—*Balance Observations in Case 6 2,200 Diet Calories*

10 Day Period No.	Dates	Nitrogen, Gm./Day: Average Urine	Average Stool	Intake	Balance	Calcium, Gm./Day: Average Urine	Average Stool	Intake	Balance	Basal Calories	B. M. R. B.	B. M. R. W.	Weight Lb.	Weight Kg.	Ht., In.	Comment
1	8/ 4- 8/21	8.45	1.54	14.15	+4.16	0.182	1.246	1.335	−0.093	1,319	+5	+9	68	30.7	56½	Rest
2	8/22- 9/ 6	8.46	1.74	14.41	+4.21	0.184	1.356	1.323	−0.054	1,347	+12	+10	70¼	31.8	..	Rest
3	9/12- 9/29	9.00	1.50	14.35	+3.75	0.133	1.012	1.208	+0.063	1,328	+5	+9	70½	31.9	..	Activity
4	11/ 7-11/24	8.47	1.25	12.87	+3.15	0.137	0.836	1.013	+0.040	1,421	+10	+13	73	33.0	..	Rest
5	11/25-12/12	8.49	1.08	12.05	+2.48	0.140	0.799	1.216	+0.277	1,419	+11	+13	73½	33.2	..	Activity

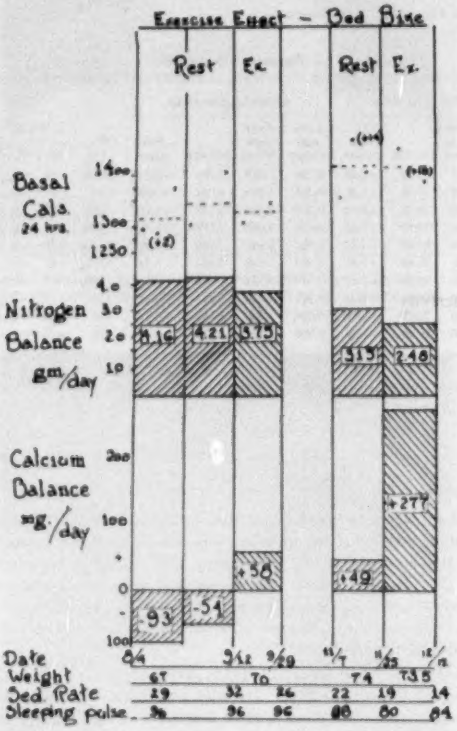

Fig. 10 (case 6).—Metabolic observations on a 13 year old boy with rheumatic heart disease.

a stationary wheel for 10 minutes three time a day while horizontal in bed. The effect of this exercise on his blood pressure was not great. A series of observations before, during and after the procedure were tabulated. The greatest change in blood pressure was the rise from 102/64 to 118/70. After a week of the exercise practically no change resulted.

The control period during the first observation showed adequate nitrogen storage, but the calcium balance was negative during a 36 day observation. It was converted to a positive balance during the 18 days of exercise, and nitrogen fell 0.46 Gm. a day. In the second observation calcium retention was slightly positive (49 mg. per day) and rose to + 277 mg. a day with exercise, whereas nitrogen fell slightly (0.67 Gm. a day).

COMMENT

We have wondered whether the prolonged rest practiced with patients with cardiac involvement, while accepted as an orthodox procedure, did not carry with it the disadvantages of demineralization. This could be offset with exercise insufficient to overtax cardiac function. Further studies on the effect of prolonged negative calcium balance on conductivity are needed.

I should stress strongly, however, that I am not prepared to compromise with rest in this condition beyond very minimal amounts, since exacerbations have been seen to follow activity when it exceeded these moderate amounts.

SUMMARY

1. In children without fever or elevation of pulse rate the retention of nitrogen and calcium is diminished by bed rest and improved with moderate activity.

2. In pulmonary tuberculosis of the reinfection type in adolescent girls, even when the temperature, pulse and basal metabolic rate are normal, rest is accompanied with increasing retentions in the first few months of treatment, after which retentions decline and may be improved with activity. It is suggested that any tendency toward diminished storage that might result from rest is offset in these children by a stronger tendency in the opposite direction to replenish depleted reserves. When this phase has passed, prolongation of inactivity would seem to result in smaller retentions than seen with moderate activity. Any anabolic effect from moderate activity may be offset when this is pushed to the point of fatigue.

3. When the horizontal position seems desirable (e. g., with tuberculosis of an upper lobe, moderate activity may be secured by the use of a single wheel bed bicycle or other apparatus.

4. Restriction of a single tuberculous joint need not compel the immobilization of the whole child.

5. It is suggested that early ambulation be part of the regimen for any chronic illness when the vital signs are normal.

Dr. O. H. Gaebler, of the Edsel B. Ford Research Institute, supervised the metabolic determinations. Dr. M. J. Sweeney and Mr. Gustav Stolz did the calcium and nitrogen determinations. Dr. V. G. Behrmann supervised the basal metabolism determinations. Dr. Paul Chapman made an independent reading of the roentgenograms.

PRIMARY COMPLEX OF PULMONARY TUBERCULOSIS

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THE GENERAL mechanism of the primary complex of pulmonary tuberculosis has been clearly understood by physicians for many years. Nevertheless many medical men, including pediatricians, have hazy and often incorrect ideas concerning its pathologic details and its clinical manifestations. The purpose of this investigation and presentation is to clarify some of the clinical and roentgen conceptions of the primary complex and coordinate them with already established anatomic and pathologic concepts.

PLAN OF THE INVESTIGATION

This investigation was carried out at St. Luke's Hospital. It is a routine procedure in the outpatient department to perform tuberculin tests, both with purified protein derivative and Vollmer patch tests, on patients 1 year of age or older. Each patient with a positive reaction is routinely observed in the following manner: the history is carefully taken, and physical examinations are then given at regular intervals; children with new lesions are examined monthly or bimonthly, and those with older lesions, at 3, 6 or 12 month intervals. The examination consists of a general evaluation of the child's health, auscultation and percussion of the chest and recording of height, weight and body temperature. Many of these examinations are supplemented by blood counts, urinalyses tests to determine sedimentation rates and gastric washings. All children are systematically and carefully followed by serial roentgenograms. Roentgenograms of lesions in the early stages are made monthly, bimonthly or quarterly. Older lesions are examined less often, usually once a year.

SCOPE OF THE INVESTIGATION

This report is based on the findings of 142 patients who first came under observation prior to December 1944; therefore, the minimum period of observation has been five years. We were not successful in keeping in contact with all these patients through the entire period, but more than half of this number were under observation throughout a period of at least five years and many for eight years or longer.

Read before the American Academy of Pediatrics, San Francisco, Nov. 16, 1949.

On this basis I present my conception of the ordinary primary complex in infants and children. I shall omit consideration of the primary or first infection type in adults. I shall also omit discussion of tuberculous meningitis and generalized miliary tuberculosis in the young, since the relation of these diseases to the primary infection is a controversial subject. By way of definition let us distinguish between the ordinary primary infection and the occasional massive primary infection which casts a large dense shadow on the roentgen film. This type of lesion has in the past usually been referred to as epituberculosis.

This report primarily concerns the ordinary primary infection, which, it is generally agreed, starts as inconspicuous parenchymal lesions which rapidly drain into the regional lymph nodes and slowly harden. Numerous testing programs [1] in various parts of the United States have indicated that at least 10 to 25 per cent of the school population contract the primary infection at some time in their growth period. I shall discuss the unusual massive primary complex only briefly and by way of contrast.

Many physicians believe that primary, or first infection, type of tuberculosis, which is synonymous with the primary complex, causes many minor disturbances of the child's health, such as fatigue, prolonged fever and cough, failure to gain weight, slowing of growth process and mild anemia or a sort of under par condition. This investigation indicates that none of these symptoms in children can be properly attributed to the ordinary or usual primary infection. Some of them may be due to the massive primary complex which casts a large dense shadow on the roentgen film.

RESULTS OF CLINICAL INVESTIGATION

None of these 142 children with the ordinary primary infection had an elevated temperature at the time of their visits which could not be accounted for by acute infection. However, Myers [2] has stated that the primary complex, although it is usually asymptomatic, may cause some fever for a limited time. None of these children at any time had a cough or rales except those accompanying an acute infection of the respiratory tract or asthma. Curves for composite weight gain and growth in height were prepared for the first consecutive 113 children of this series and superimposed on curves for a control group of outpatients. The weight gain and growth curves of the control group were identical with the curves of those who had primary tuberculosis (figs. 1 to 4).

1. Myers, J. A.: Tuberculosis Among Children and Young Adults, ed. 2, Springfield, Ill., Charles C Thomas, 1938, p. 146.

2. Myers, J. A.: Primary Tuberculosis, in Hayes, E. W.: Fundamentals of Pulmonary Tuberculosis and Its Complications, Springfield, Ill., Charles C Thomas, Publisher, 1949, p. 45.

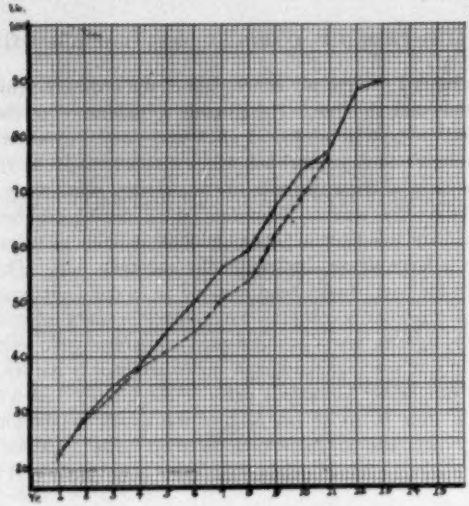

Fig. 1.—The solid line indicates the weights of boys whose reactions for tuberculosis are positive. The broken line indicates the weights of boys whose reactions are negative.

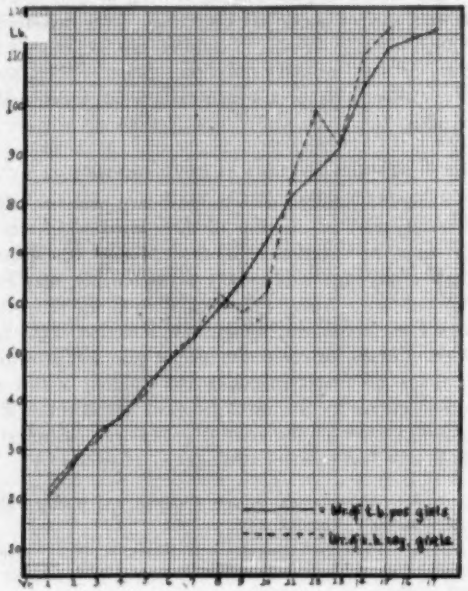

Fig. 2.—The solid line indicates the weights of girls whose reactions for tuberculosis are positive. The broken line indicates the weights of girls whose reactions are negative.

The average red blood cell count for this group of 113 children with primary tuberculosis was 4,100,000, the average white blood cell count 7,500 and the average hemoglobin level 13.2 Gm. There were no controls. However, these values do not differ materially from those of the average children encountered in the clinic.

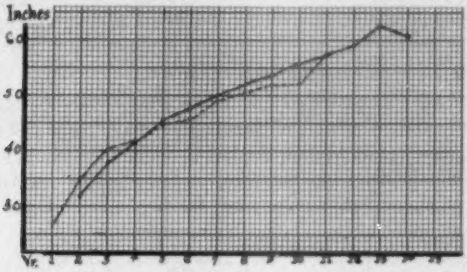

Fig. 3.—The solid line indicates the heights of boys whose reactions for tuberculosis are positive. The broken line indicates the heights of boys whose reactions are negative.

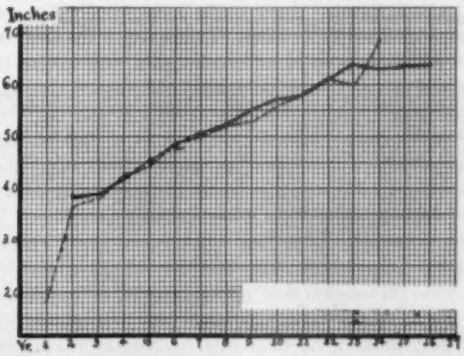

Fig. 4.—The solid line indicates the heights of girls whose reactions for tuberculosis are positive. The broken line indicates the heights of girls whose reactions are negative.

At least one determination of the sedimentation rate (Cutler method) was done on 84 of the entire group of 142. If a fall of 15 mm. the first hour is taken as the upper limit of normal, only 13 per cent of the sedimentation rates were abnormally high. This percentage is insignificant from a diagnostic standpoint. One or two normal sedimentation rates in the course of a chronic disease is by no means sufficient evidence to conclude that an acceleration of the sedimentation rate may not occur

at some time in the course of the disease. Gastric washings with direct examination and guinea pig inoculation of the sediment were performed on 52 children with the primary infection. For the most part children were selected whose lesions showed no evidence of calcification, and most of these 52 were not among the group of 142 which form the main basis of this report. Results of all these tests were negative. The significance of these findings will be discussed in the section on treatment.

ROENTGEN FINDINGS

The following roentgenologic picture of the primary complex slowly emerged after study of the serial roentgenograms of these 142 cases over a period of eight years. Within the last two years the films of each case have been withdrawn from the files, and studied in retrospect, each case being reviewed individually from the beginning. Each individual film was read in connection with the roentgenologist's report for that film. A roentgen summary of each case was tabulated. Therefore the composite description which is to follow is primarily that of the roentgenologist, who was not informed as to the results of the tuberculin tests in these children.

The roentgen features of the primary complex are inconspicuous and are not characteristic. In a single roentgenogram these shadows cannot be distinguished from many shadows cast by acute pulmonary disease. However, a positive tuberculin skin reaction taken in conjunction with slowly changing pulmonary shadows is diagnostic of the primary complex.

Typically the primary complex appears as soft diffuse shadows in one or more lobes. They appear to radiate from the hilus into the parenchyma but do not extend as far as the chest wall. Care must be exercised in distinguishing them from vascular markings. These soft diffuse shadows usually make their roentgen appearance in more than one lobe at the same time. However not all parenchymal shadows necessarily make a simultaneous appearance. The appearance of one lesion may lag a relatively short time behind the others. The upper lobes in the first and second intercostal spaces anteriorly are the most frequent sites for these shadows. The lower lobe of the right lung is the next most frequent location. The lesions may appear in the apex of either lung, but this is an infrequent location. Within a few weeks after the peripheral shadows appear, the hilar shadows become prominent, indicating hilar node enlargement. The hilar node involvement occurs so soon after the parenchymal infection that one seldom finds a patient with peripheral shadows without hilar node involvement. These nodular masses may appear as soft rounded shadows with clearly defined edges, but much more frequently they appear as a diffuse enlargement or prominence of the hilar shadows (figs. 5 and 6).

The peripheral shadows harden over a period varying up to two or three years and end as inconspicuous but definite linear shadows representing scar tissue. As the child grows into adolescence, the chest

Fig. 5.—Roentgenogram of a 31 month old child with a positive reaction, illustrating the early stage of an entirely asymptomatic ordinary primary complex. Note the bilateral soft parenchymal shadows and soft nodular mass at the right hilus.

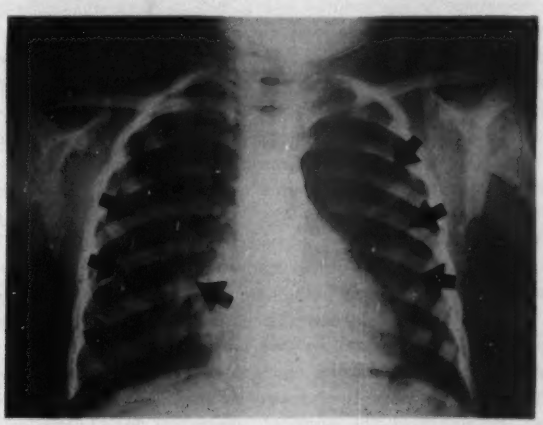

Fig. 6.—Roentgenogram of the same child as in figure 5, taken 10 months later. Note the clearing and hardening of all shadows. No treatment was given.

thickens and these delicate linear shadows fade to the point where they are often indistinguishable from normal bronchovascular markings.

During this time enough calcium to be detected roentgenologically may have been deposited in one or more of these parenchymal lesions. The deposit may be single, but it is usually multiple. Such deposits are by definition Ghon tubercules. These deposits of calcium, detected by roentgen rays in the parenchyma of the lungs, occurred in only 25 per cent of 88 cases which were followed by serial roentgenograms for five years or longer. From the standpoint of roentgen examination the presence of the Ghon tubercle must be considered the exception rather than the rule.

While the peripheral or parenchymal lesions are hardening, the hilar nodes are also undergoing the same slow process. These changes in the hilar nodes, progressing over a period of years, are most easily followed by observing the calcification process. Although roentgen evidence of peripheral calcification is the exception, hilar node calcification is decidedly the rule. It occurred in 93 per cent of the 88 cases followed by roentgenograms for five years or longer. The length of time required for roentgen evidence of calcification to begin and to end is of interest. In only 34 cases were the serial films begun early enough and taken with sufficient regularity and frequency to warrant assigning the time of the first appearance of the calcium in the hilar nodes. On the basis of these 34 cases calcium usually appeared between one and four years after the time hilar node enlargement was first noted. The peak of the curve was at two years. The extreme limits of the curve were a minimum of six months and a maximum of five years before calcium first appeared in the lymph nodes. To repeat, two years was the usual length of time required for roentgen evidence of calcium in the hilar nodes to appear. After their first appearance the calcium deposits usually grew denser over a period of one, two or three years. There is therefore abundant roentgen evidence that the tissue changes of the ordinary primary complex are of great chronicity. As the child goes into adolescence and the thicker chest itself obstructs more roentgen rays, the calcium deposits become less conspicuous on subsequent roentgenograms.

These roentgen findings of the primary complex may be obscured by the shadows of other chronic pathologic conditions of the chest, such as asthma or cardiovascular disease. They may be obscured by or resemble acute pulmonary disease on any one roentgenogram. There is a lag between the time the tuberculin reaction first becomes positive and the appearance of shadows on the roentgenograms, but, with due allowance for these circumstances, the primary complex, in our experience, regularly manifests itself in serial roentgenograms.

Summarizing the roentgen description of the primary complex, the lesions occur first in the parenchyma of one or more lobes, usually simultaneously, and rapidly drain into corresponding hilar nodes, as

evidenced by increased prominence of the hilar shadows. After this both the central and the peripheral lesions harden slowly over a period of years and finally become static. The hilar nodes eventually calcify in 90 per cent or more of these patients, whereas peripheral calcification or Ghon tubercle formation occurs in only 25 per cent (fig. 7).

THE MASSIVE PRIMARY COMPLEX

The foregoing clinical and roentgen description of the ordinary primary complex should be sharply contrasted with the more spectacular but far less frequent primary lesion which casts massive pulmonary shadows on the roentgenogram. Although this massive type is frequently discussed in the literature, it is rarely encountered in general pediatric practice. Only three such cases have been encountered in the course of this study, and in two of these the patients came directly to the children's ward of the hospital. As pointed out above, the children with the ordinary primary infection had no clinical symptoms by which it could be detected or suspected. In contrast these 3 children with the massive primary complex did have symptoms which caused them to come to the hospital, but the symptoms were relatively mild when considered in conjunction with the roentgen shadows; furthermore, the shadows persisted months after the symptoms disappeared.

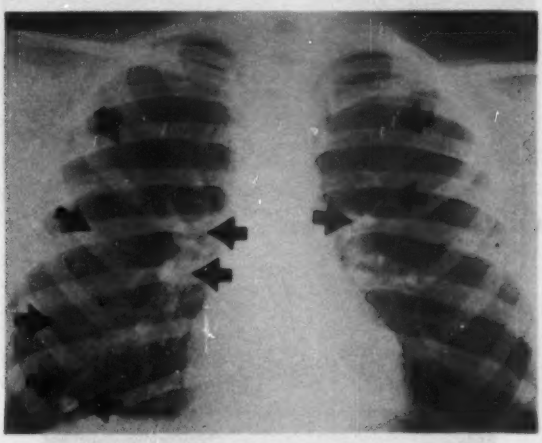

Fig. 7.—Roentgenogram of a 12 year old child with a positive reaction, illustrating a well healed primary complex. Note the delicate linear scars in the upper lobe of each lung and the lower lobe of the right lung. Also note calcium deposits in the hili and the sixth interspace on the right (Ghon tubercle).

The children with the massive primary complex were said to have coughed a few days or weeks before entering the hospital. Two were

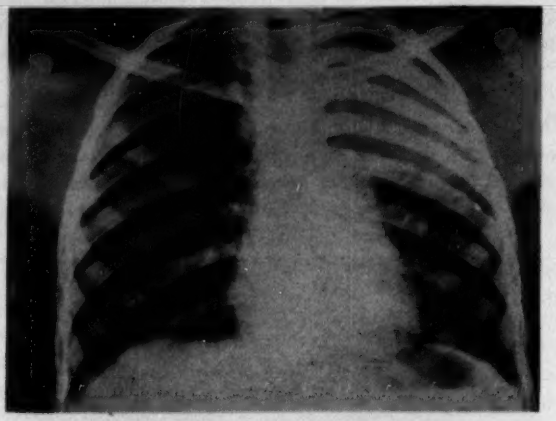

Fig. 8.—Roentgenogram of a 10 year old child with a positive reaction, illustrating the exceptional massive primary complex (epituberculosis). Dulness was marked, rales few and symptoms mild.

Fig. 9.—Lateral view of the lesion in figure 8.

thought to have lost weight. However, after entering the hospital they did not appear debilitated; they ate well and played happily. There was only a little coughing, and when fever was present it was of low grade. The roentgen findings varied, but in each case there was a conspicuous

shadow involving a considerable portion of one lobe. Tubercle bacilli were identified in each child by guinea pig inoculation but not by direct smear. Material for inoculation was obtained from gastric washings or directly from the bronchial tree through the bronchoscope (figs. 8, 9 and 10).

These three cases have been briefly described to emphasize their relative infrequency when compared with the ordinary primary complex, and to point out that the children did have clinical symptoms. These symptoms were mild when compared with those of other pulmonary diseases casting comparable shadows. One is not justified in

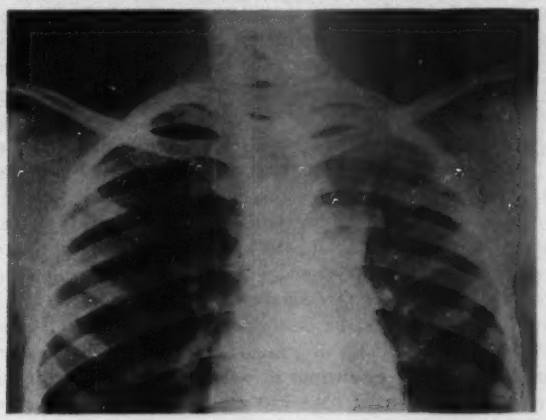

Fig. 10.—Roentgenogram of the same child as in figures 8 and 9, taken 10 months later. Note the clearing with heavy linear scars in the upper lobe of the left lung.

drawing general conclusions from such a small group, although the evidence does seem suggestive.

TREATMENT

For the purpose of treatment it seemed wise to separate the two groups.

The much larger group without symptoms and with inconspicuous roentgen shadows received no treatment except removal from the source of their infection, if it was known. A carefully taken history revealed the source in only slightly more than one third of these cases. As to rest and food, the mothers of these children were instructed to do only those things that are generally recommended for normal children.

Myers,[3] speaking from a large experience, stated that the primary infection does not need to be treated in a preventorium and that fever, if present, may be treated by bed rest at home or in a general hospital.

The small group with symptoms and massive shadows received symptomatic treatment during their hospitalization. No drug therapy was used except in the case of one patient, who was given 1 Gm. of streptomycin daily for thirty days. This short course of streptomycin seemed not to influence the symptoms or the rate of resolution.

The question of isolation had to be faced. Although I have never obtained evidence of tubercle bacilli by spot checking a considerable number of ordinary primary infections by guinea pig inoculation, it cannot be concluded that in such infections tubercle bacilli are never discharged into the bronchial tree. A number of investigators, cited by Rich,[4] have reported that by this method they recovered tubercle bacilli from children with asymptomatic primary lesions. It does seem unlikely that a great number of organisms are discharged regularly. This idea is substantiated by clinical experience. Myers [3] stated that since "persons with primary tuberculosis usually do not have cough or sputum, the danger of contamination is practically nil." Rich,[5] in his masterful treatise, "The Pathogenesis of Tuberculosis," stated, after reviewing the bacteriologic and pathologic evidence, that in the primary infection the bacilli multiply rapidly and unhampered for a short time but that the body defense processes soon bring the infection under control and usually sterilize the caseous primary lesion. It is generally agreed that not all primary lesions are thus sterilized. For practical reasons I decided not to attempt to isolate the children with the ordinary primary infection. I have had no reason to regret this decision. Those with massive primary infections were isolated while in the hospital.

SUMMARY AND CONCLUSIONS

During the last eight years I have closely observed 142 children with the ordinary primary complex of pulmonary tuberculosis, both clinically and roentgenologically. More than half were under observation for a minimum period of five years. Evidence has been presented to indicate that for practical clinical purposes the overwhelming majority of these primary tuberculous infections of the lungs in infants and children are entirely asymptomatic. They produce no demonstrable effect on the child's general well-being. They can be detected only by a combination of skin tests and serial roentgenograms. The latter is the

3. Myers,[2] p. 49.

4. Rich, R.: The Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1944, p. 898.

5. Rich,[4] pp. 482-484.

only effective means of observing their progress. The primary complex of pulmonary tuberculosis begins as parenchymal lesions, usually multiple, which drain rapidly into the corresponding hilar nodes. Both the peripheral and the central lesions heal slowly with calcium deposits in the hilus in about 90 per cent of these children. Peripheral calcium deposits or Ghon tubercle formations occur in about 25 per cent of them. Although the primary infection is rapidly brought under control by the body defenses, the tissue changes, as evidenced by roentgen observation, progress for a period measured in years rather than months. During the course of this investigation three children with primary infections were encountered who did have some clinical symptoms. The pulmonary lesions in each case cast massive roentgen shadows, and in each case tubercle bacilli were demonstrated by guinea pig inoculation.

Children with the ordinary primary complex need no treatment except removal from the source of infection. It seems impractical and unnecessary to isolate children with ordinary primary infections. On the other hand, those with the massive primary infection should be treated symptomatically. They should be isolated as long as tubercle baccilli can be recovered from gastric washings.

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RESPIRATORY ACIDOSIS IN CHILDREN WITH CEREBRAL, PULMONARY AND CARDIOVASCULAR DISORDERS

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ALTHOUGH there have been numerous communications on the more commonly found metabolic disturbances of acid-base balance, as well as on respiratory alkalosis, reports of cases of respiratory acidosis have been meager in the pediatric literature.[1] However, with a specific search among patients who might be predisposed to it, not infrequently instances of respiratory acidosis may be found. It is the purpose of this report to describe 16 cases of this entity observed at the Children's Hospital of Buffalo and to call attention to the important fact that unless it is suspected and correctly diagnosed incorrect therapy may ensue.

Uniformity of concentration and reaction of body fluids is controlled largely by renal function with the exception of the plasma carbon dioxide content, which is controlled mainly by the respiratory mechanisms.[2] The normal p_H of the blood must be maintained within the narrow limits of 7.35 to 7.45 in order to protect the normal vital physiochemical processes of cell metabolism. From the Henderson-Hasselbalch equation it is seen that the normal p_H of 7.40 is maintained when the ratio $BHCO_3 : HHCO_3$ is 20:1, regardless of the absolute values of the individual components of the buffer system. Either a fall in $BHCO_3$ or a rise in $HHCO_3$, and particularly a combination of the two, will

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1. (*a*) Spector, S., and McKhann, C. F.: Respiratory Acidosis and Alkalosis in Children, J. Pediat. **32**:227 (March) 1948. (*b*) Brühl, H.: Studien zur physikalischchemischen Atmungsregulation und zum Säurebasengleichgewicht beim Kinde, in Atmungsregulation und Säurebasenhaushalt bei der Tetanie der Rachitiker, Basel, S. Karger, 1944, chap. 2.

2. (*a*) Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus, ed. 4, Cambridge, Mass., Harvard University Press, 1942. (*b*) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945.

result in a fall of the p_H. Because of the 20:1 ratio it may be seen that any apparently small retention of H_2CO_3 will decrease the value of the ratio considerably, and an apparently paradoxical state develops in which a normal plasma bicarbonate level is associated with a low p_H. By retaining $BHCO_3$, the organism is able to revert the $BHCO_3$: $HHCO_3$ ratio, and thereby the plasma p_H, toward normal, with the result that a high plasma bicarbonate level and normal p_H are observed. These conditions are interpreted as respiratory acidosis, uncompensated or compensated, because the retention of H_2CO_3 (or CO_2) is due to failure of the respiratory mechanism which is responsible for maintaining the normal carbon dioxide tension of the plasma. The carbon dioxide tension of the blood parallels the alveolar carbon dioxide tension except under conditions in which the diffusion of this gas through the alveolar membranes is impaired and equilibration thereby prevented. Because of the relation expressed in the Henderson-Hasselbalch equation and discussed above, the $HHCO_3$ of the blood will for the purpose of this paper be expressed in milliequivalents per liter rather than as carbon dioxide tension in millimeters of mercury, which may be measured in the alveolar air.

The normal respiratory functions may be disturbed in various pulmonary and some cerebral disorders. Anoxemia, manifested by cyanosis, usually attracts the attention of the physician and presents an urgent therapeutic problem. It should, however, be remembered that under certain conditions retention of carbon dioxide may be associated with deficient oxygenation of the blood and may occasionally even be aggravated rather than relieved by intensive oxygen therapy. The situations in which respiratory acidosis may occur may be divided roughly into four categories:

I. Conditions in which there is suppression of respirations
   1. Damage to the central nervous system
      a. Brain damage (trauma, inflammation or compression) and convulsions
      b. Drug poisoning (for example, by morphine or barbiturates)
      c. Excessive anesthesia
      d. Bulbar poliomyelitis
   2. Loss of "ventilatory function"[3] of the lung itself due to increased intrathoracic pressure or loss of elasticity
      a. Tension cysts
      b. Tension pneumothorax
      c. Pulmonary and mediastinal tumors
      d. Emphysema
   3. Effect of pain (pleurisy)

3. Baldwin, E. de F.; Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency: I. Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects, Medicine **27**:243 (Sept.) 1948.

II. Conditions characterized by impairment of diffusion of carbon dioxide across the alveolar membrane (reduced "alveolo-respiratory function" [2])
   1. Reduction of the respiratory surface
      a. Emphysema
      b. Pulmonary fibrosis (cystic fibrosis of the pancreas and lungs)
   2. Thickened alveolar membranes or exudates
      a. Severe pulmonary infiltration (for example, in bronchopneumonia and pertussis)
      b. Pulmonary edema
      c. Congenital alveolar dysplasia

   In severe pneumonia both mechanisms may operate.

III. Conditions in which there is an obstacle to the escape of carbon dioxide from the alveoli
   1. Obstruction in the respiratory tract
      a. Laryngeal obstruction (croup, edema or spasm due to trauma or tetany)
      b. Foreign body
      c. Bronchiolitis
      d. Asthma
   2. Rebreathing from a closed space
   3. A continuous stream of oxygen being delivered into the trachea under pressure through an intratracheal tube

IV. Conditions in which the pulmonary blood flow is insufficient
   1. Certain types of congenital heart disease (for example, pulmonary stenosis or atresia with a right to left shunt)
   2. Ayerza's disease.

Sixteen cases of respiratory acidosis are reported here as examples of the four categories listed above.

METHODS

Venous blood for determination of p_H, carbon dioxide content and chlorides was obtained anaerobically under liquid petrolatum, allowed to clot, centrifuged and immediately analyzed. Arterial blood was obtained anaerobically, heparin being used as an anticoagulant and sodium fluoride as a preservative; it was collected and centrifuged over mercury. Noncentrifuged portions of the samples were used for oxygen determinations in some cases. These samples were cooled immediately and kept cold until analyzed. The urine specimens were mostly fresh and collected without special precautions, although a few were 24-hour specimens collected under toluene.

Chemical Methods.—The p_H of the serum was determined anaerobically with the McInnes microglass electrode and the Cambridge Instrument Company potentiometer. The determination was done at room temperature, and Nims's correction [4] was applied to calculate the p_H at 38 C. The potentiometer was standardized each time with a potassium biphthalate solution of p_H 4.00. Phosphate buffers in the range of the blood p_H were checked on several occasions and were always found to be accurate within 0.00 to 0.03. The p_H of the urine was determined with Accutint indicator paper. The carbon dioxide content of the serum was

4. Personal communication from L. F. Nims, cited by Pitts, R. F., and Alexander, R. S.: The Nature of the Renal Tubular Mechanism for Acidifying the Urine, Am. J. Physiol. **144**:239 (July) 1945.

determined by the standard Van Slyke manometric technic, with use of 0.2 cc. of serum. The carbonic acid was calculated from the p_H and the carbon dioxide content. The chlorides were determined in 0.1 cc. of serum by Van Slyke's direct silver nitrate–nitric acid method. Total protein in the serum was in most cases determined with Lowry's gradient tube,[5] although in some cases micro-Kjeldahl digestion and nesslerization were used. The total fixed bases of the serum were determined by electrodialysis into boric acid. Oxygen content and capacity of the arterial blood were determined in 2 cc. samples by the standard Van Slyke manometric technic. The results of the chemical analyses are listed in the table, and diagrams of the electrolyte composition of representative blood specimens are shown in the chart.

REPORT OF CASES

The first five cases illustrate respiratory acidosis due to depression of the respiratory center. Case 3 is described in detail.

Case 1.—M. O., an 8 year old girl, was admitted in a comatose state on Feb. 27, 1949 because of measles encephalitis with convulsions. Chemical analysis of the blood (table) showed respiratory acidosis (p_H 6.96). The first specimen was drawn within 10 minutes after a convulsion, when the patient was faintly cyanotic and had irregular shallow respirations. Her convulsions were then controlled with intravenous amobarbital sodium (amytal sodium®) and ether anesthesia. Her respiratory depression was treated with stimulants, artificial respiration, oxygen and pharyngeal suction. Two hours after admission she responded and became delirious and boisterous. Her respirations became much fuller at this time; she quieted down within a few hours and then made a rapid recovery. A blood specimen on the second hospital day had a normal p_H.

This patient had an acute episode of respiratory acidosis due to central depression of respirations in measles encephalitis with convulsions; the acidosis corrected itself spontaneously.

A similar mechanism apparently operated in the case described next.

Case 2.—R. P., a 14 month old boy, was admitted on Feb. 7, 1949 as a comatose, dehydrated baby with tonic and clonic convulsive movements and noisy respirations. The rectal temperature was 38.9 C. (102 F.). The respiratory rate was 11 and the pulse rate 120 a minute. The impression on admission was that the baby had febrile convulsions, bronchopneumonia and bilateral catarrhal otitis media. Chemical study of the blood on admission (table) revealed a respiratory acidosis (p_H 7.09). The patient was given antipyretics and amobarbital sodium intravenously and was placed in an oxygen tent. Chemotherapy was begun. On this regimen the patient no longer had convulsions, his breathing improved, and by the third hospital day his temperature was normal.

Case 3.—L. S., an 11 month old girl, was admitted on Sept. 27, 1949, with a history of persistent irregular fever and intermittent tonic convulsions of three months' duration and severe diarrhea for 24 hours.

Physical Examination.—The physical examination revealed a desperately ill, dehydrated, ashen gray and cyanotic baby, comatose, convulsing, with very shallow irregular respirations. Her rectal temperature was 41.3 C. (106.3 F.); her pulse

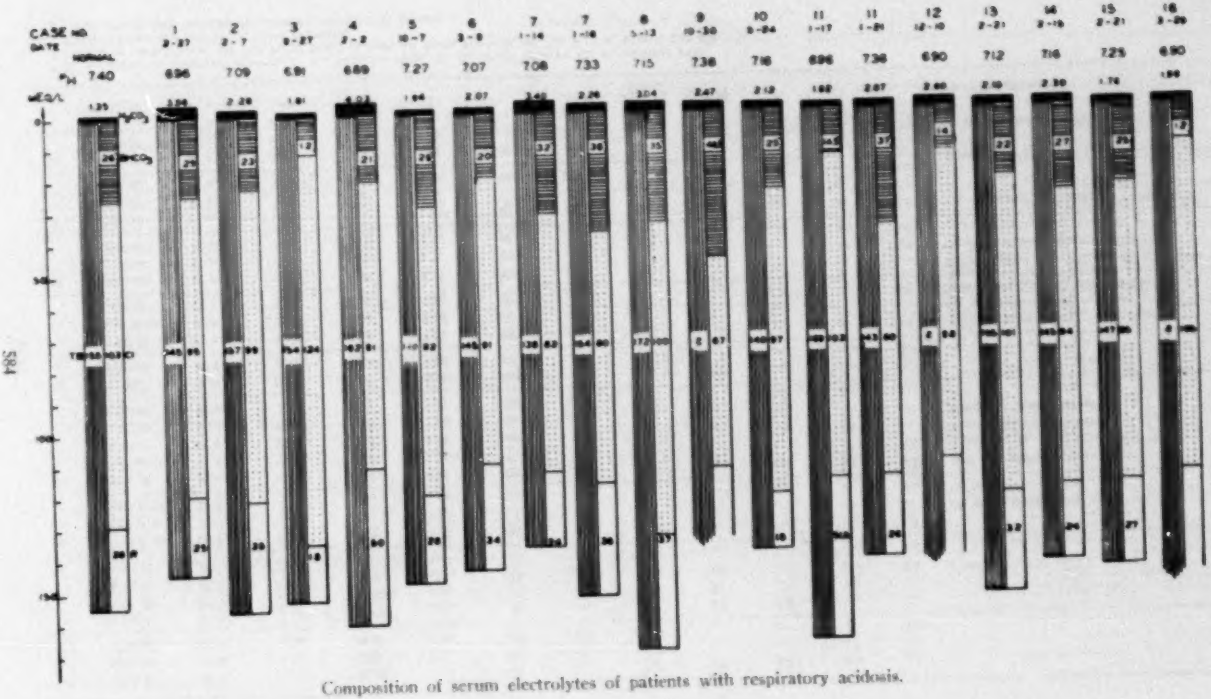
5. Lowry, O. H., and Hunter, T. H.: The Determination of Serum Protein Concentration with a Gradient Tube, J. Biol. Chem. **139**:462 (July) 1946.

Chemical Data of Cases

Case	Date	Source*	Blood: p_H	Blood: CO_2 Content, mEq./L.	Blood: H_2CO_3, mEq./L.	Blood: Cl, mEq./L.	Blood: Total Base, mEq./L.†	Blood: Total Protein, Gm./100 Cc.	Blood: N. P. N., Mg./100 Cc.	Blood: Ca, Mg./100 Cc.	Blood: P, Mg./100 Cc.	Urine, p_H	Remarks
1	2/27/40	F. a.	6.96	28.6	3.96	95	145	...	..	...	...	6.0	Comatose; infrequent shallow respirations
	2/28/40	F. a.	7.37	24.6	1.27	88	...	...	..	...	...	...	
2	2/ 7/40	F. v.	7.00	25.0	2.28	99	157	...	33	8.7	...	...	Convulsions; depressed respirations
3	9/27 a. m.	F. a.	6.91	13.5	1.81	124	(154)	6.2	43.4‡	10.5	7.9	...	Respirations very shallow, with pauses
	9/27 2 p. m.	F. a.	7.05	13.6	1.36	..	...	...	..	...	...	5.5	Respirations irregular, periodic, fairly deep
	9/27 8 p. m.	F. a.	7.25	12.4	0.82	108	...	4.4	..	...	...	...	Marked hyperventilation
	9/28/40	F. a.	7.32	15.8	....	103	(139)	...	15.8‡	8.3	...	5.5	Specimen contaminated with air
4	2/ 2/40	F. v.	6.89	24.8	4.08	91	162	...	39	8.5	...	5.5	Gasping respirations, 4 a minute
	2/ 2/40 p. m.	F. v.	7.26	25.0	1.60	89	...	...	..	...	...	...	Normal respirations
5	10/ 7/40	F. a.	7.27	30.8	1.94	92	(140)	...	..	...	...	6.0	.....
6	3/ 9/40	F. v.	7.07	21.8	2.07	91	145	5.8	19	...	...	...	.....
	3/10/40	F. v.	7.26	25.4	1.62	91	143	6.4	28	...	...	...	.....
	3/14/40	F. v.	7.29	26.7	1.92	91	...	5.8	..	...	...	...	.....
	3/16/40	F. a.	7.28	24.4	1.45	92	157	...	..	...	...	...	O_2 saturation, 89%
	3/22/40	F. v.	7.23	22.8	1.56	81	...	6.5	..	...	...	...	.....
	3/26/40	F. v.	7.25	23.5	1.55	93	...	...	..	...	...	5.9	.....
	4/ 4/40	F. a.	7.37	28.5	1.42	98	...	6.6	..	...	...	6.0	O_2 saturation, 81%
	4/ 8/40	F. a.	7.38	30.6	1.06	97	...	...	..	...	...	...	O_2 saturation, 86%
	4/26/40	F. v.	7.20	22.0	1.60	89	...	6.7	..	...	...	5.3	.....
	5/ 6/40	F. a.	7.25	19.1	1.36	93	...	6.5	..	...	...	...	O_2 saturation, 81%
7	1/14/40	F. v.	7.08	35.2	3.4	82	136	6.9	44	...	...	5.5	Heart failure; coma
	1/15/40	F. v.	7.23	37.8	2.57	82	...	...	43	...	...	...	.....
	1/16/40	F. v.	7.33	40.5	2.26	80	154	...	37	9.2	...	6.0	.....
	1/17/40	F. v.	7.14	40.0	3.28	74	...	...	..	8.6	...	...	.....
	1/19/40	F. v.	7.34	38.4	2.11	93	...	...	..	...	...	...	.....
	1/25/40	F. v.	7.26	33.6	2.14	87	156	...	..	...	...	6.0	.....

8	5/ 5/48	F. v.	....	20.0‡	....	108	...	5.6	54	9.3	4.4	...	.....
	5/ 7/48	F. v.	....	33.8	....	101	...	...	..	...	...	...	.....
	5/13/48	F. v.	7.15	38.0	2.04	100	172	...	..	...	...	7.0	.....
9	10/24/47	F. v.	....	27.0‡	....	96	...	...	26	8.9	...	...	.....
	10/27/47	F. v.	....	37.0‡	....	75	...	4.9	37	...	...	...	.....
	10/29/47	F. v.	....	46.0	....	76	...	4.6	32	...	...	5.4	.....
	10/30/47	F. v.	7.38	49.0	2.47	67	...	...	..	...	...	5.0	.....
10	5/24 a. m.	C. v.	6.97	29.4	3.50	96	...	3.1	..	...	...	...	.....
	5/24 p. m.	F. a.	7.16	27.2	3.12	97	140	...	..	...	...	...	O_2 saturation, 80%
	5/24 p. m.	F. v.	7.10	....	....	..	...	...	..	...	...	...	.....
11	1/17/49	F. v.	6.96	16.4	1.92	105	169	...	..	7.0	8.4	4.5	Severely dehydrated
	1/17 p. m.	F. v.	7.21	20.3	1.44	..	...	...	..	...	...	5.5	After fluids, including $NaHCO_3$
	1/21/49	F. v.	7.36	39.0	2.07	80	143	...	..	7.0	2.4	...	Frequent convulsions
	1/26/49	F. v.	7.37	35.6	1.78	80	140	...	..	5.3	...	...	Frequent convulsions
	1/28/49	F. v.	....	33.2	....	76	152	...	..	10.7	...	...	.....
12	12/10/48	F. v.	6.99	16.7	2.00	98	...	7.2	88‡	...	...	5.0	.....
	12/11/48	F. v.	7.03	18.5	1.96	102	...	6.2	..	...	...	6.0	.....
13	2/21/49	F. v.	7.17	21.4	1.65	101	155	...	..	...	...	5.3	After tracheotomy
	2/21 p. m.	F. a.	7.12	24.4	2.10	101	155	...	..	...	...	...	O_2 saturation, 79%
	2/24/49	F. v.	7.46	24.2	1.02	97	...	...	..	...	...	6.0	After coughing up membrane
14	2/15/49	F. v.	7.16	29.2	2.30	94	145	...	..	...	...	...	Retractions; respirations 92 a minute
	2/16/49	F. a.	7.25	26.0	1.71	95	...	...	..	...	...	5.7	O_2 saturation, 88%
	2/17/49	F. v.	7.45	28.1	1.21	93	...	...	..	...	...	5.9	.....
15	2/21/49	S. a.	7.25	27.9	1.76	95	147	...	..	...	...	5.9	.....
	2/23/49	F. v.	....	31.4	....	..	...	5.1	27	8.4	...	...	.....
	2/24/49	F. a.	7.26	28.6	1.83	103	149	...	..	...	...	6.4	.....
16	3/29/49	F. a.	6.90	14.3	1.96	105	...	9.5	76	...	...	...	.....
	3/30/49	F. a.	7.14	20.9	1.75	..	...	...	16	...	...	...	O_2 saturation, 14.9%
	4/ 7/49	F. a.	7.39	....	....	..	...	...	..	...	...	...	.....
	4/11/49	F. a.	7.40	23.4	1.13	..	...	...	5.8‡	...	...	...	O_2 saturation, 55%

* F. a. indicates femoral artery; F. v., femoral vein; S. a., scalp artery; C. v., cubital vein.
† Values in parentheses are for total base, calculated from the sum of Na, K, Ca, plus 3 for Mg.
‡ These values are for blood urea nitrogen.
§ These values are for carbon dioxide—combining power.



Composition of serum electrolytes of patients with respiratory acidosis.

rate, 118 a minute. The pupils were equal and constricted. There was pooling of mucus in the pharynx. Coarse rhonchi were heard scattered throughout the chest.

Laboratory Examination.—The hemoglobin content was 10.5 Gm. per 100 cc. The cerebrospinal fluid contained 11 leukocytes per cubic millimeter. Results of the chemical analysis of three specimens of arterial blood taken under varying conditions on the first hospital day are listed in the table and show a combination of metabolic and respiratory acidosis (p_H 6.91 on admission). The p_H rose as the respirations improved, while the carbon dioxide content remained at the low level of 12 to 13 milliequivalents per liter. A culture of the blood remained sterile.

Course.—Artificial respiration and oxygen were immediately administered, and amobarbital sodium, 64 mg., was injected intravenously in order to control the convulsions but was only partially successful. The first blood sample was taken immediately after the amobarbital sodium injection, when the respirations were very shallow with long apneic pauses. During the next three hours the hydration and respirations improved slightly under therapy consisting of fluids given intravenously, another dose of amobarbital sodium and constant alcohol sponging to combat the hyperpyrexia. After a second blood specimen had been drawn, three to four hours after the first one (table), 240 cc. of M/6 sodium lactate solution was slowly infused. Ten hours after admission the baby was hyperventilating vigorously, and examination of another specimen of arterial blood showed that now she was blowing off carbonic acid and the p_H of her plasma had been thereby raised, although the bicarbonate content was still unchanged. The metabolic acidosis was subsequently corrected by the intravenous administration of sodium bicarbonate. The patient's temperature remained at a high level, and her urinary output remained scanty. On the second hospital day she had periods of apnea alternating with hyperpnea, and artificial respiration had to be applied several times. She died 44 hours after admission. The postmortem examination revealed diffuse swelling of the brain, which weighed 1,266 Gm. (normal weight 852 Gm.), and recent catarrhal enterocolitis with lymphadenitis of the intra-abdominal lymph nodes.

In this patient respiratory acidosis, due to depression of the respiratory center by convulsions and possibly the amobarbital sodium injection, complicated and aggravated a metabolic acidosis secondary to diarrhea and oliguria. As the respirations improved with therapy, the respiratory acidosis subsided before the metabolic component.

Case 4.—L. K., a 15 month old girl, was admitted on Feb. 2, 1949 because of stupor and convulsions for 2½ hours. Because of some fever, she had been given two proprietary pills (containing 0.3 mg. of aconite and Veratrum viride each) the night before admission and three more the morning of admission. Within an hour after the second dose her breathing became irregular and labored and her hands and lips cyanotic. She seemed disoriented and began to have convulsions and was hospitalized two hours later. The patient was a stuporous infant with bilateral convulsive movements and very infrequent gasping respirations, about four a minute. The diagnosis was thought to be febrile convulsions or possibly aconite poisoning. Chemical analysis of the blood on admission (table) showed a glucose content of 202 mg. per 100 cc. and the existence of respiratory acidosis (p_H 6.89). Six hours later the serum p_H had risen to 7.26.

Course.—The child was given stimulants and chemotherapy and remained comatose and oligopneic for two hours. Her pulse rate and temperature fell by lysis, and her breathing became normal on the second day.

This is another case of acute, self-limited respiratory acidosis due to depression of the respiratory center. In this case drug poisoning was considered to be responsible for either direct depression of the center, with anoxia resulting in convulsions, or primary convulsions acting on the respiratory center.

CASE 5.—J. T., a 7 year old girl, was admitted on Oct. 4, 1949, with a diagnosis of bulbar poliomyelitis. On her third hospital day she became unable to take even fluids by mouth because of swallowing difficulty, and all subsequent alimentation was given parenterally. She had increased puddling of pharyngeal secretions and gradually became irrational and semistuporous. When on her fourth hospital day she seemed to have a poor pulmonary air exchange, with physical signs suggesting atelectasis, a tracheotomy was performed. A specimen of arterial blood taken just prior to the tracheotomy revealed a respiratory acidosis (p_H 7.27, table). After the tracheotomy the patient continued to breathe shallowly and went steadily downhill. She died 30 hours postoperatively. The postmortem examination revealed moderate alveolar and interstitial emphysema and extensive atelectasis of the lungs. There was marked swelling and hyperemia of the brain.

In this case respiratory acidosis was associated with progressive depression of the respiratory and all other medullary centers by poliomyelitis. Three other instances of mild respiratory acidosis, two of them compensated, were observed in nonfatal cases of bulbar poliomyelitis in the same epidemic.

CASE 6.—C. H., an 8 month old boy, was admitted on March 9, 1949 because of cough and fever for 10 days. He was admitted to the Children's Hospital because of failure to respond to antibiotic therapy and because roentgenograms of his chest suggested the presence of three large air-filled cavities with fluid levels.

Physical Examination.—The rectal temperature on admission was 38.6 C. (101.5 F.); the pulse rate 120 and the respirations 56 a minute. This was a well developed and well nourished infant looking acutely ill, with a hacking cough, dyspnea and slight cyanosis. Respirations were labored, with flaring of the alae nasi. The percussion note over the right upper part of the chest was dull to flat, and over the right lower part of the chest it was tympanitic. The entire left side of the chest was hyperresonant. Posteriorly over the right lung there were amphoric breath sounds with a high-pitched metallic tinkle. Inspiratory rales were heard faintly over the upper part of the right side of the chest anteriorly. No mediastinal shift was noted on percussion. The remainder of the physical findings were normal. The admission diagnosis was congenital cystic disease of the lungs with superimposed infection.

Laboratory Examination.—The urine on admission was normal (p_H was not determined). A tuberculin test elicited a negative reaction. Roentgenographic and fluoroscopic examination of the chest and abdomen revealed multiple air pockets in the right side of the chest. The largest cavity measured 8.5 by 7 by 5 cm. and contained a fluid level. The esophagus was pushed to the left. There was a small amount of fluid at the apex of the right lung and no evidence of right lung function. Chemical analysis of the blood (table) revealed a respiratory acidosis (p_H 7.07 on admission) which persisted to a minor degree for over a month. Determination of the oxygen saturation of the arterial blood on several occasions revealed a saturation of between 81 and 89 per cent.

Course.—The patient was put into an oxygen tent and given penicillin and sulfadiazine. His fever subsided, but amphoric breath sounds and signs of atelectasis persisted over the upper lobe of the right lung. Over the next month he gradually improved, and his chest roentgenograms showed considerable reduction in the size of the cavities. The physical signs of increased intrathoracic pressure disappeared simultaneously with the return of the blood p_H to normal. The respiratory rate throughout this period was 40 to 50 a minute at rest. On April 27, the fiftieth hospital day, a thoracotomy was performed on the right side for an intended pneumonectomy. However, instead of the expected lung cysts, extrapulmonary, intrapleural cavities lined with thick fibrous layers of organized exudate were found. The whole collapsed right lung was bound down by fibrous tissue into the posterior medial third of the right side of the chest. After the fibrous tissue was peeled off the lung surface the right lung could be reexpanded under positive pressure. The postoperative course was smooth; the child did not have respiratory acidosis, and his respiratory rate decreased to as low as 25 a minute during sleep.

In this patient a mild, though uncompensated, respiratory acidosis was maintained over a prolonged period, probably owing to the fact that the intrapleural tension cysts (which originally must have been part of a pyopneumothorax) caused increased intrathoracic pressure, resulting in rapid shallow breathing with insufficient air exchange.

The children in the second group of six cases (7 through 12) had severe degrees of pulmonary infiltration and/or fibrosis, resulting in impaired diffusion of gases through the alveolar membrane. Case 7, being the most illustrative of the group, is presented in detail.

Case 7.—G. H., a 7 year old girl, was admitted on Jan. 13, 1949, with the chief complaints of dyspnea for one week and generalized cyanosis and oliguria for 24 hours. When the child was 6 months old, a diagnosis of celiac disease had been made. From the age of 30 months on she had had many episodes of infection of the upper respiratory tract, bronchitis and bronchopneumonia. At the age of 6 years a persistent cough, productive of copious thick sputum, developed. In 1948, clubbing of her fingers and cyanosis of her nail beds were noted. Analysis of her duodenal secretions revealed the absence of trypsin, and the diagnosis of cystic fibrosis of the pancreas was established. Despite a course of streptomycin intramuscularly, penicillin by aerosol and sulfadiazine orally, the child became progressively more dyspneic and fatigued. On Jan. 5, 1949, she became dyspneic even while in bed. On the day before admission to the hospital her lips became cyanotic, and she failed to urinate for 24 hours.

Physical Examination.—The rectal temperature was 37.1 C. (98.8 F.); the pulse rate was 120, and respirations were 60 a minute. The patient was a thin pale girl looking chronically and acutely ill and in a semistupor. Her skin was ashen gray and faintly cyanotic. Her lips and mucous membranes were parched. Her veins were distended. There were moist crepitant inspiratory rales heard throughout the chest, and there was dulness to percussion over the entire chest and flatness at the bases of both lungs. The air exchange was very poor. The heart sounds were rapid and faint, but no murmur or cardiac enlargement was noted. The blood pressure was 110 systolic and 76 diastolic. The liver was enlarged and tender. There was pitting ankle edema. The admission diagnoses were cystic fibrosis of the pancreas with pulmonary fibrosis, acute diffuse interstitial pneumonia,

acute cardiac failure secondary to chronic pulmonary fibrosis and acute infection, and acute renal failure.

Course, Therapy and Laboratory Examination.—The patient was placed in an oxygen tent, given a clysis of 5 per cent dextrose in water and six hours later voided 300 cc. of acid urine (p_H 5.5). However, the next morning she became comatose. A blood specimen drawn then (table) revealed a pronounced respiratory acidosis (p_H 7.08). The venous pressure was 285 mm. of water. Consequently, an attempt was made to relieve her pulmonary congestion by digitalization and to treat her pneumonia with penicillin. On her third hospital day (January 15) the patient was conscious, voided freely and breathed more slowly, and her color improved. A blood specimen at this time showed a lessening of the acidosis (p_H 7.23) and correction of the hypoelectrolytemia (table). On her fourth hospital day the child continued to improve. Chemical examination of her blood showed the respiratory acidosis to be compensated and the p_H to be raised by an increase of the plasma bicarbonate level. The salt intake was increased. After oral aureomycin therapy was started on the patient's eighth hospital day, her respirations seemed much easier and her pulse rate fell to below 100 a minute. She was discharged much improved on her twenty-fourth day and has led a comfortable normal existence up to the time of this writing.

The respiratory acidosis in this patient was chronic and presumably caused by the marked reduction of respiratory surface which occurs with pulmonary fibrosis. It was acutely aggravated when the exudate of acute pneumonia and heart failure further impaired the exchange of respiratory gases. At times this acidosis was compensated, that is, the p_H was rendered normal by a marked increase of the plasma bicarbonate, but the carbonic acid (H_2CO_3) content of the blood always remained considerably elevated, and the urine remained acid.

At a later date an almost identical picture, although with less extreme laboratory findings, was observed in a 2 year old child with known cystic fibrosis of the pancreas during an episode of acute pneumonia and heart failure.

CASE 8.—F. S., a 3 week old boy, born prematurely, was admitted on May 5, 1948 because of cough, dyspnea and cyanosis. He was a small, marasmic, dehydrated infant with bronchopneumonia and otitis media. Cultures of material taken from the nose, throat and trachea showed growth of Pseudomonas aeruginosa. Chemical analysis of the blood on admission revealed an essentially normal composition save for an elevated nonprotein nitrogen level (table). A blood specimen obtained two days before death revealed respiratory acidosis with a p_H of 7.15.

Course.—During the night following admission the baby had a sudden cessation of respirations and a pulse rate of 4 to 5 a minute. With artificial respiration, suction and stimulants the baby was revived. He gradually became more dyspneic and cyanotic. On the ninth and tenth hospital days bronchoscopy and aspiration were performed, with temporary relief. The baby died on the eleventh hospital day. Postmortem examination revealed bilateral bronchopneumonia due to Ps. aeruginosa, with complete atelectasis of the right lung, compensatory emphysema of the left lung and mediastinal shift to the right.

In this case bronchopneumonic exudate and atelectasis had left almost no respiratory surface exposed to air; consequently respiratory acidosis and anoxia resulted from the impaired diffusion of gases in the alveoli.

CASE 9.—C. I., a 3 month old girl, was admitted on Oct. 24, 1947 because of pertussis with cyanosis, dyspnea and coma. The diagnoses on admission were pertussis, bronchopneumonia and possible encephalitis. Chemical analyses of the blood are listed in the table. The plasma bicarbonate level in the course of six days rose from 27 to 49 milliequivalents per liter with a simultaneous fall of the chlorides to 67 milliequivalents per liter. The serum p_H was determined on the day before death (Oct. 30, 1947) and was found to be 7.38. There had been no vomiting and no administration of bicarbonate which could have caused metabolic alkalosis. Therefore, because of the clinically apparent disturbance of respiratory function, the chemical data were interpreted as depicting compensated respiratory acidosis. The low p_H of the urine (5.0) was confirmatory.

Course.—The patient had a stormy course, marked by extreme dyspnea, convulsions and frequent episodes of apnea, with or without attacks of paroxysmal cough, alternating with tachypnea. Artificial respiration had to be given on frequent occasions, and large amounts of tenacious mucus were suctioned from the throat. She grew progressively worse and died on the eighth hospital day. Postmortem examination showed confluent lobular pneumonia and bronchopneumonia of all lobes, with alveolar emphysema in the intervening lung tissue. There was moderate generalized edema and slight meningeal hydrops. Neither hemorrhage nor conspicuous hyperemia was seen in the brain.

In this case, too, reduction of the exposed alveolar surface may have been chiefly responsible for the retention of carbon dioxide. Central depression of respirations due to encephalitis may have contributed to the disturbance.

CASE 10.—M. S., a 12 year old girl, was admitted on May 21, 1949 because of high fever, cough, emesis and cervical lymphadenopathy. The patient was a cyanotic, desperately ill girl with rapid shallow respirations, a dry hacking cough and physical signs of extensive pulmonary infiltration. There was generalized anasarca and cervical and inguinal lymphadenopathy. Chemical analysis of the blood on the last hospital day revealed hypoproteinemia and a marked respiratory acidosis (p_H 6.97, table). Throughout her hospital stay the child was extremely dyspneic and orthopneic. On her fourth hospital day she died. Postmortem examination revealed generalized Hodgkin's disease with generalized granulomatous infiltration of both lungs in addition to bacterial pneumonitis.

CASE 11.—W. B., an 8 week old boy, was admitted on Jan. 17, 1949, with the diagnosis of bronchopneumonia, parenteral diarrhea and meningitis due to Hemophilus influenzae type B. On admission the rectal temperature was 41.1 C. (106 F.); the pulse rate was 160 and respirations 70 a minute. The patient was a critically ill infant with dry cyanotic skin. Shortly after admission he had a generalized convulsion. Chemical analysis of the blood revealed a severe acidosis (p_H 6.96) which was thought to be of both metabolic and respiratory origin (table).

Course.—The child was treated with intravenously administered fluids, chemotherapy, type-specific anti-H.-influenzae serum, continuous oxygen and calcium gluconate. His acidosis was corrected with 3.0 Gm. of sodium bicarbonate given intravenously during the first 24 hours. On the second hospital day he had a sudden collapse, with irregular shallow breathing. For the next 15 hours he required constant artificial respiration. The patient then gradually improved chemically (table) and physically.

In this case as well as in the following one retention of carbonic acid, probably mainly due to the pneumonic infiltration of the alveoli,

was added to the loss of bicarbonate caused by diarrhea and dehydration. The combination of these two factors resulted in an extreme depression of the blood p_H.

CASE 12.—W. D., a 2 year old child with mongolism and congenital heart disease, showed also a combination of bronchopneumonia, heart failure and severe dehydration which resulted in a combined respiratory and metabolic acidosis with the extremely low p_H of 6.90 (table). Urine studies, including clearance studies, revealed damage of renal function for over a month.

In the next 3 cases (13 through 15) the patients had obstruction of the respiratory passages which interfered with the escape of carbon dioxide.

CASE 13.—J. B., a 5 month old boy, was admitted on Feb. 20, 1949 because of fever, cough, anorexia and rapidly increasing dyspnea and restlessness.

Physical Examination.—On admission the baby was acutely ill, with dilating alae nasi and marked sternal retractions. The rectal temperature was 40.5 C. (104.9 F.); the pulse rate was 180, and respirations were 40 a minute. Auscultation of his chest revealed poor aeration and numerous fine crepitant inspiratory rales in the right lung field. The heart sounds were of good quality. The liver was slightly enlarged. The diagnoses of laryngotracheobronchitis and bronchopneumonia were made on admission.

Laboratory Examination.—The p_H of the admission urine specimen was 5.5. Culture of tracheal secretions revealed a coagulase-positive Staphylococcus aureus. Chemical analysis of the blood (table) taken nine hours after tracheotomy revealed a respiratory acidosis (p_H of the arterial blood 7.12) and an arterial oxygen saturation of 78.5 per cent.

Course.—The patient was placed in a steam tent, but after six hours he was not improved. His respiratory rate had increased to 100 a minute. A tracheotomy was performed which gave little relief. The patient had a stormy course, with intermittent cyanosis, shock, stupor, restlessness, convulsions and heart failure. On the third hospital day (February 22) he coughed up a complete membranous cast of his tracheobronchial tree and thereafter recovered progressively. Two days after the obstruction had been relieved the respiratory acidosis was shown to have corrected itself (table).

In this patient obstruction of the trachea and bronchi interfered with elimination of carbon dioxide, causing respiratory acidosis. The obstruction was suddenly relieved when the patient coughed up the obstructing membrane. A sudden release of carbonic acid presumably occurred, and the p_H rose from 7.12 to 7.46.

CASE 14.—E. H., a 6 week old girl, was admitted on Feb. 14, 1949 because of cough and dyspnea for four days. The rectal temperature was 37.8 C. (100 F.); the pulse rate was 130 and the respirations 58 a minute. There was an expiratory dyspnea with decreased respiratory excursions and a hacking cough. A provisional diagnosis of bronchiolitis was made, and the patient was put into an oxygen tent. On the day after admission suprasternal and infrasternal retractions developed, the patient breathing 92 times a minute. Auscultation of her chest revealed a very poor air exchange and many rales. Chemical analysis of the blood (table) showed a respiratory acidosis (p_H 7.16). A specimen of arterial blood

taken on the third hospital day when the patient had improved had an oxygen saturation of 88 per cent. A roentgenogram of the chest showed a patch of bronchopneumonia in the upper lobe of the right lung and some emphysema. Her dyspnea and physical and chemical signs gradually improved within the next week.

The acute respiratory acidosis in this patient was produced by a mechanism similar to that in the previous case except that the obstruction may have been located mainly in the finer bronchi and bronchioli rather than in the upper parts of the respiratory tree. The same mechanism is assumed to have played a role in the following case.

CASE 15.—M. K. a 6 week old boy born prematurely, was admitted with evidence of acute bronchiolitis with emphysema and dehydration secondary to vomiting and signs of respiratory and circulatory failure. Chemical analysis of the arterial blood (table) revealed a mild respiratory acidosis (p_H 7.25). His respiratory distress diminished over a period of two weeks.

CASE 16.—N. K., a 17 month old girl with known cyanotic congenital heart disease, was admitted on March 29, 1949 because of increasing dyspnea, cyanosis and lethargy. On the morning of admission she had had a seizure characterized by unconsciousness, foaming at the mouth, increasing cyanosis and extreme dyspnea.

On admission the patient was an underdeveloped and poorly nourished, deeply cyanotic infant with air hunger. The rectal temperature was 37.2 C. (99 F.) on admission but rose to 38.8 C. (101.8 F.) within a few hours; the pulse rate rose from 110 to 140 a minute shortly after admission; the respiratory rate was 45 a minute. The blood pressure was 85 systolic and 50 diastolic. Her scleras were injected, with dilated veins. The pharynx and drum membranes were inflamed. The percussion note over the lung fields was resonant throughout; no rales were heard. The heart was slightly enlarged toward the left. The sounds were of good quality; no murmurs were heard. The liver and spleen were enlarged. There was marked clubbing of the fingers and toes. The impression on admission was that the patient had congenital heart disease (probably tetralogy of Fallot) in failure, a respiratory infection and respiratory acidosis

Laboratory Examination.—The urine was normal. Study of the blood revealed a hematocrit reading of 76 per cent, a hemoglobin content of 16.5 Gm. per 100 cc. and a red cell count of 6,700,000 per cubic millimeter. Chemical analysis of the blood (table) revealed a combined respiratory and metabolic acidosis (p_H 6.90). On the day after admission the oxygen saturation of the arterial blood was 14.8 per cent. Subsequent studies revealed a normal p_H and an oxygen saturation of 35 per cent. A blood culture remained sterile. A chest roentgenogram showed an enlarged heart; the lungs were clear. Roentgenograms of the bones revealed a bone age of 9 months. Fluoroscopic findings, together with an electrocardiogram which showed evidence of left axis deviation and left ventricular hypertrophy, suggested a diagnosis of rudimentary right ventricle associated with tricuspid atresia and pulmonary stenosis.

Course.—The patient was placed in an oxygen tent, sedated and given digitalis. She was also given penicillin and 450 cc. of M/6 sodium lactate by mouth during the first eight hours. Under this therapy her dyspnea subsided in part, and within five days she seemed improved. On her fourteenth hospital day anastomosis between her aorta and left pulmonary artery was established surgically. She was still cyanotic and tachypneic six hours after the operation, when she was

thought to be in cardiac failure. She died 15 hours postoperatively. A necropsy was performed; it revealed the operative anastomosis to be intact and functionable. The heart was enlarged and globular, with a rudimentary right ventricle. There was no auricular septum. The pulmonary artery was patent, but there was complete tricuspid atresia. The trachea and major bronchi were full of aspirated bile and stomach contents. The child apparently died from asphyxia due to aspiration.

COMMENT

The diagnosis of respiratory acidosis is made on finding a low plasma p_H combined with a high $HHCO_3$ (or carbon dioxide tension), the latter value having been calculated in this study from measurements of p_H and carbon dioxide content.

It is important that the blood specimens as nearly as possible represent the condition of the blood as it bathes the respiratory center directly. The blood should be collected anaerobically, ideally over mercury; however, if liquid petrolatum is used, the specimens should be analyzed immediately after collection or the oil should be previously saturated with carbon dioxide, since carbon dioxide diffuses through liquid petrolatum to a certain degree. Arterial blood should be used whenever possible. If venous blood is used, it should be taken from the internal jugular vein, since this blood is returning directly from the respiratory center and differs least from arterial blood in that it contains less carbon dioxide than does venous blood from a limb.[6] In cases of disturbance of the respiratory center the blood in the venous sinuses of the dura is said to reflect conditions in the respiratory center more accurately than arterial blood.[1b] It has also been pointed out by Douglas and Havard [7] that it is essential that the arterial puncture be done quickly and painlessly in order to avoid disturbing the subject, since that might lead to a sudden alteration in breathing. Obviously, in children this can be achieved only if local anesthesia is used or the patient is unconscious, as were many of our patients. Douglas and Havard were concerned with much smaller deviations of p_H and carbon dioxide tension than the ones observed in the cases here discussed. However, it is conceivable that vigorous crying and struggling might produce considerable changes, in both directions, of p_H and carbon dioxide tension, partly because of overbreathing and partly because of lactic acid production.

The extreme reduction of the p_H of the serum of some of the patients in the present study calls for special comment. In seven patients p_H values below 7.0 were observed, three of them in arterial blood (in cases 1, 3 and 16) and the others (in cases 4, 10, 11 and 12) in venous blood

6. Haldane, J. S., and Priestley, J. G.: Respiration, ed. 2, 1935, New Haven, Yale University Press, 1935, p. 385.

7. Douglas, C. G., and Havard, R. E.: The Changes in the CO_2 Pressure and Hydrogen Ion Concentration of the Arterial Blood of Man Which Are Associated with Hyperpnea Due to CO_2, J. Physiol. **74**:471 (April) 1932.

from a limb; the lowest value observed was 6.89. Such low values have until recently been thought to be incompatible with survival and recovery, although Singer and Hastings [8] defined the "extreme pathological limits" as 6.7 to 7.9. Retention of even small amounts of carbon dioxide causes a lowering of the p_H much more readily than does an excess of fixed acids, especially in acute conditions, since none of the other compensatory mechanisms work as rapidly as the respiratory one. It might therefore be expected that lower p_H values would be found in respiratory acidosis than in metabolic acidosis. Draper, Whitehead and Spencer [9a] have produced severe respiratory acidosis with p_H values as low as 6.70 (average 6.78) in dogs under the extreme condition of "diffusion respiration," in which respiratory movements were abolished by thiopental sodium but oxygenation of the blood was maintained by previously filling the respiratory space with pure oxygen. These authors made the interesting observation that at the peak of respiratory acidosis the carbon dioxide content was higher and the p_H lower in the arterial than in the venous blood, while during the recovery period there was a reversal to the normal relation.[9b] Eleven of the 12 dogs recovered completely and permanently after 45 to 90 minutes of diffusion respiration. In human subjects Altschule and Sulzback [10] by a similar procedure have produced a respiratory acidosis with a p_H of 6.89 which was also followed by recovery. Eastman reported p_H values of 6.95 to 7.12 associated with a high carbon dioxide tension in the blood of the umbilical veins of six asphyxiated infants, three of whom died.[11] All the patients seen by us who had a serum p_H value below 7.0 were comatose and in acute, severe severe respiratory failure. The extreme depression of the p_H was always transitory; repeat examination after five to 24 hours revealed a rise to above 7.10 in every case except case 12, in which the p_H rose to only 7.03. In cases 3, 11, 12 and 16 metabolic acidosis contributed to the lowering of the p_H.

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8. Singer, R. B., and Hastings, A. B.: An Improved Clinical Method for the Estimation of Disturbances in the Acid-Base Balance of Human Blood, Medicine **27**:223 (May) 1948.

9. (*a*) Draper, W. B.; Whitehead, R. W., and Spencer, J. N.: Studies on Diffusion Respiration: III. Alveolar Gases and Venous Blood p_H of Dogs During Diffusion Respiration, Anesthesiology **8**:524 (Sept.) 1947. (*b*) Whitehead, R. W.; Spencer, J. N.; Parry, T. M., and Draper, W. B.: Studies on Diffusion Respiration: IV. The Oxygen and Carbon Dioxide Content and the Hydrogen Ion Concentration of Arterial and Venous Abdominal Blood of Dogs During Diffusion Respiration, Anesthesiology **10**:54 (Jan.) 1949.

10. Altschule, M. D., and Sulzback, W. M.: Tolerance of the Human Heart to Acidosis; Reversible Changes in the RS-T Interval During Severe Acidosis Caused by the Administration of Carbon Dioxide, Am. Heart J. **33**:458 (April) 1947.

11. Eastman, N. J.: Fetal Blood Studies: III. The Chemical Nature of Asphyxia Neonatorum and Its Bearing on Certain Practical Problems, Bull. Johns Hopkins Hosp. **50**:39 (Jan.) 1932.

The mechanisms involved in the 16 cases here reported should be considered.

When there is suppression of respirations, asphyxia with its concomitant hypercapnia and lowered p_H results. The patients often die of the anoxia, but with intensive oxygen therapy the anoxia may be relieved and the hypercapnia persist. Hypercapnia without anoxia following or during inhalation of 100 per cent oxygen has been observed not only during the above cited experiments with diffusion respiration [9] but also during barbiturate anesthesia [12] and voluntary breathholding.[13] In cases 1, 2, 3 and 4 the respirations were depressed to 4 to 12 a minute because of cerebral damage. Case 3 offers a striking illustration of the control of the p_H by the respiration; in three observations within 11 hours the p_H rose from 6.91 at the time of irregular shallow infrequent respirations through 7.05 during a phase of periodic breathing to 7.25 during marked hyperventilation, while the bicarbonate content of the serum, which had been lowered by the effects of diarrhea, remained unchanged. In case 5 the respiratory rate was normal, but the respiratory movements were shallow. In case 6 the respiratory rate was increased, but the tidal air, minute volume and vital capacity (measured by crude methods) were reduced as a result of the increased intrathoracic pressure. With a low tidal volume the mixing of the gases in the lungs would be poor. In such circumstances the exchange of carbon dioxide is interfered with more extensively than the oxygen exchange, owing to the greater diffusibility of the smaller oxygen molecules in a gaseous medium.[14] Concomitant with a reduction of respiratory embarrassment, the improvement as shown by the chest roentgenogram and the increase in ventilatory function, there was a reduction of respiratory acidosis.

The diffusion coefficient of carbon dioxide across the alveolar membrane is 11 to 20 times greater than that of oxygen at rest and 16 to 23 times greater during exercise or labored breathing.[2b] Therefore, in cases in which the diffusion of gases is impaired by the presence of exudate in the alveoli or thickening of the alveolar membrane, respiratory acidosis is rarely seen before anoxia has reached a degree which endangers the patient's life. If, in addition, the respiratory surface is diminished extensively, so that exchange of both gases is interfered with, respiratory acidosis may result. In most of our cases classified in group II (cases 7

12. Moyer, C. A., and Beecher, H. K.: Effects of Barbiturate Anesthesia (Evipal and Pentothal Sodium) upon the Integration of Respiratory Control Mechanisms, J. Clin. Investigation **21**:429 (July) 1942.

13. Ferris, E. B.; Engel, G. L.; Stevens, C. D., and Webb, J.: Voluntary Breathholding: III. The Relation of the Maximum Time of Breathholding to the Oxygen and Carbon Dioxide Tensions of Arterial Blood, with a Note on Its Clinical and Physiological Significance, J. Clin. Investigation **25**:734 (Sept.) 1946.

14. According to Graham's Law, the diffusion coefficient of CO_2 is 0.139 sq. cm. per second; of O_2, 0.178 sq. cm. per second.

through 12) both reduction of the exposed respiratory surface and increase of the distance between the alveolar air and the pulmonary capillaries were present. In three of the six cases of this group (8, 9 and 10) the patients died and the postmortem examination showed practically all their alveoli filled with exudate; consequently, the alveolar surface exposed to inspired air was practically nil. In cases 11 and 12 similar mechanisms may have been at work. In case 7 extensive fibrosis of the lungs was demonstrated roentgenographically. This condition is known to result in a considerable decrease of the alveolar surface. Even after the acute infection and pulmonary edema of heart failure had disappeared, persistent respiratory acidosis gave further evidence of this anatomic disturbance.

With obstruction in the respiratory passages, expiration and thereby elimination of carbon dioxide is frequently interfered with more seriously than inspiration. An increased alveolar carbon dioxide tension and therefore an increased retention of carbon dioxide in the blood will result. Such a mechanism is assumed to have been operating in cases 13, 14 and 15, in all of which there was obstruction of the larger or finer bronchi. In case 13 the obstruction was suddenly relieved after the patient coughed up a membranous cast of his bronchial tree. In such cases a sudden release of carbon dioxide may occur and result in an abrupt rise of the $BHCO_3 : HHCO_3$ ratio and thereby of the p_H value. In cases of compensated respiratory acidosis, in which the plasma bicarbonate level is elevated, a metabolic alkalosis may result.[14] This did not happen in case 13 because the patient's respiratory acidosis was uncompensated, but the p_H rose from 7.12 to 7.46.

One would expect patients with severe reduction of pulmonary artery blood flow and a right to left intracardiac shunt to have interference with the exchange of both oxygen and carbon dioxide by a mechanism similar to that which operates in patients with reduced respiratory surface. Although the blood gases in the pulmonary vein are presumably in equilibrium with the alveolar air, the blood coming from the lungs constitutes but a small portion of the systemic blood flow. Thus, one would expect to find a high carbon dioxide tension and a low oxygen tension in the arterial blood. Actually, in the literature respiratory acidosis has not been reported in patients with cyanotic congenital heart disease. Most of the patients with cyanotic heart disease who were studied had metabolic acidosis,[15] a low basal metabolic rate and high levels of organic acids in the blood. The low metabolic rate may possibly counteract the tendency toward retention of carbonic acid, since less

15. Talbott, J. H.; Coombs, F. S.; Castleman, B.; Chamberlain, F. L.; Consolazio, W. V., and White, P. D.: A Record Case of the Tetralogy of Fallot, with Comments on Metabolic and Pathologic Studies, Am. Heart J. **22**:754 (Dec.) 1941.

carbon dioxide is produced than in normal patients of the same size. The low basal metabolic rate, according to Bing,[16] is presumably the result of metabolic adjustment to prolonged anoxemia. The presence of unusually large amounts of reduced hemoglobin may be another factor in preventing respiratory acidosis in these patients, by virtue of its buffering activity. In patient 16, in whom the bronchial arteries provided the only access for blood to the pulmonary capillaries, the oxygen saturation of the arterial blood (15 per cent) was much lower than in any of the patients (none with saturation under 57 per cent) studied by Bing,[16] Talbott and others [18] and the various authors referred to by them. The patient's hematocrit reading was 72 per cent. Her oxygen consumption was not measured but can be assumed to have been extremely low. The retardation of her growth and development may be taken as evidence of her low metabolic activity. Nevertheless, at a time when the patient had fever (temperature 38.8 C., 101.8 F.), an ear infection and labored respirations, p_H values of 6.90 and 7.14 were observed in her arterial blood on two occasions which, according to calculation, must have been due to a combination of high H_2CO_3 and low $BHCO_3$. It is suggested that during the febrile episode the child's metabolic rate was so increased that more carbon dioxide was formed than could be eliminated from her lungs. Probably there was also an increased lactic acid production. After the temperature returned to normal and the heart failure subsided, the carbon dioxide and p_H of the blood returned to normal levels. The bicarbonate content also rose as a result of sodium lactate therapy.

COMPENSATORY MECHANISMS

Retention of carbonic acid produces a reduction of the blood p_H approximately 20 times more readily than retention of an equivalent amount of fixed acid. The following physiological mechanisms may protect the body from this change in p_H.

1. The chloride shift. There is a shift of chloride ions from the plasma into the red blood corpuscles which has been shown to occur within a few minutes after the experimental retention of carbon dioxide and lowering of p_H.

2. The excretion of chloride in the urine. This process requires a longer time.

Both of these mechanisms result in a lowering of the chloride content of the plasma (which in one of the patients here reported reached a level of 67 milliequivalents per liter) and thereby make more base available to form bicarbonate.

16. Bing, R. J.; Vandam, L. D.; Handelsman, J. C.; Campbell, J. A.; Spencer, R., and Griswold, H. E.: Physiological Studies in Congenital Heart Disease: VI. Adaptations to Anoxia in Congenital Heart Disease with Cyanosis, Bull. Johns Hopkins Hosp. **83**:439 (Nov.) 1948.

3. A further increase in bicarbonate. As a result of an absolute increase of fixed base in the body additional bicarbonate can be made available by the renal mechanisms of excreting an acid urine and of replacing fixed base with ammonium ions.

4. The buffering capacity of hemoglobin. Under physiological conditions this mechanism is constantly used to allow the transport of approximately 2 milliequivalents of carbonic acid from the tissues to the lungs without appreciable change in the p_H and is effective in the cases of respiratory acidosis associated with anoxia. This mechanism can be assumed to be particularly effective in patients with high hematocrit values and hemoglobin levels and low arterial oxygen saturation.

5. Stimulation of depth and rate of respiration. This stimulation, due to the effect of increased carbon dioxide tension and decreased p_H of the blood directly on the respiratory center and of anoxia on the aortic and carotid body chemoreceptors, helps the body to blow off carbon dioxide. However, the causes which lead to respiratory acidosis usually prevent this mechanism from being very effective under the conditions discussed here.

In cases of primary disturbance of the respiratory center respiratory acidosis may be very acute and correct itself spontaneously as the condition of the center improves. When retention of carbon dioxide is caused by local pulmonary conditions, respiratory acidosis will persist as long as the local factors in the lungs persist; in some such cases it may become chronic.

THERAPEUTIC CONSIDERATIONS

The most rational and effective therapy of respiratory acidosis is the relief of the basic cause of the condition. When there is suppression of respirations on a central basis, artificial respiration (manually or by respirator) or stimulant drugs may serve to remove the accumulated carbon dioxide. Chemotherapy and digitalis may help patients in whom the respiratory surface is reduced by inflammatory exudates or edema. In patients in whom there is obstruction of the respiratory passages, this should be relieved, if possible.

When the basic cause cannot be corrected, symptomatic therapy may be attempted. In those patients in whom the total base is low, there is theoretical advantage in giving sodium bicarbonate or sodium lactate during the acute phase. Knowing the p_H and the carbon dioxide content of the patient's serum, one might calculate by the Henderson-Hasselbalch equation the amount of bicarbonate necessary to correct the p_H to an arbitrary safe level (for example, 7.20 or higher). The calculated amount should be administered slowly and cautiously, with checking of the p_H and carbon dioxide content of the blood at frequent intervals. The results

cannot be predicted as closely as in metabolic acidosis, and metabolic alkalosis produced by excessive doses of bicarbonate might prove more difficult to treat and more dangerous than mild respiratory acidosis. Chlorides should not be given during respiratory acidosis, even if the serum chloride level is low, in order not to defeat the compensatory mechanisms which tend to lower the plasma chloride and make more base available to form bicarbonate. However, in the event of a sudden release of carbon dioxide after relief of respiratory obstruction, sodium or calcium chloride should be pushed. This is especially important in cases of compensated respiratory acidosis with high bicarbonate levels.

Giving carbon dioxide for inhalation to anoxic patients suffering from respiratory acidosis is, of course, contraindicated, since the body is already overloaded with this gas. Giving more carbon dioxide in such circumstances may result in raising the carbon dioxide content of the blood to a narcotizing level at which respirations will be inhibited rather than stimulated.

Practically all the causes of respiratory acidosis also result in anoxia. Every one of our patients was cyanotic at some time, and in each of five cases in which the oxygen saturation of the arterial blood was determined it was below 89 per cent. Schmidt [17] showed that in the presence of anoxia the respiratory center is depressed rather than stimulated by the usual respiratory stimulants, such as atropine, camphor and caffeine, as well as carbon dioxide. Therefore, oxygen therapy is an essential part of the treatment of all patients with respiratory acidosis. It may be important to consider here the fact, demonstrated by Marshall and Rosenfeld,[18] that in patients with severe depression of the respiratory center, for example, by anesthetics, who depend on the anoxemic stimulus to the carotid sinus and aortic mechanisms, administration of oxygen may abolish this stimulus and thereby produce further depression of respirations. If the oxygen tension of the arterial blood is above 70 mm. of mercury (which corresponds to an arterial oxygen saturation of about 92 per cent), the carotid sinus and aortic mechanisms will fail to maintain respiratory movements.[19] Theoretically, this consideration may limit the indication for oxygen therapy in certain cases, and means for artificial respiration should be at hand. However, we have not encountered adverse effects of oxygen therapy in our clinical material.

17. Schmidt, C. F.: The Influence of Cerebral Blood Flow on Respiration: I. The Respiratory Responses to Changes in the Cerebral Blood Flow, Am. J. Physiol. **84**:202 (Feb.) 1928.

18. Marshall, E. K., Jr., and Rosenfeld, M.: Depression of Respiration by Oxygen, J. Pharmacol. & Exper. Therap. **57**:437 (Aug.) 1936.

19. Schmidt, C. F., and Comroe, J. H., Jr.: Functions of the Carotid and Aortic Bodies, Physiol. Rev. **20**:115 (Jan.) 1940.

SUMMARY

Sixteen cases of respiratory acidosis are presented with clinical and laboratory data.

A classification of the causative mechanisms is suggested.

In five cases respirations were suppressed on a cerebral basis and in one case by increased intrathoracic pressure. In six cases diffusion of carbon dioxide across the alveolar membrane was impaired by reduction of the respiratory surface or thickened alveolar membranes or both. In three cases there was obstruction of the respiratory passages. In one case of congenital heart disease the pulmonary blood flow was insufficient.

In seven cases the p_H of the serum was observed to be below 7.0; in four of these cases the respiratory acidosis was associated with metabolic acidosis.

Physiological compensatory mechanisms are discussed.

The principles of therapy are considered.

Drs. Raymond S. Filsinger, Richard A. Downey, A. Wilmot Jacobsen and Kenneth M. Alford gave permission to include the cases of their private patients (cases 7, 9, 14 and 16 respectively) in this study.

Case Reports

PERFORATION OF DUODENUM BY INGESTED FOREIGN BODY

Symptoms Suggesting Disease of the Hip

JAMES B. GILLESPIE, M.D.

URBANA, ILL.

In most instances in which indigestible foreign bodies are swallowed, the objects will pass uneventfully through the entire intestinal tract of either children or adults. The possibility of ulcerative penetration by sharp, elongated or pointed objects in the intestinal tract, however, necessitates careful and continued observation in every case. So long as the intruder keeps moving downward, there is little danger.

The occurrence of perforation of the intestine from ingested foreign bodies is not common. In a series of 800 cases reported from the Boston City Hospital, perforation occurred in only 1 per cent.[1] Not a single instance of perforation occurred in a group of 41 children of pediatric age who had swallowed foreign bodies of different types, and in every child the object was passed spontaneously.[2] It has been concluded from another series of 386 cases that 90 per cent of swallowed foreign bodies will pass spontaneously.[3] In one instance a foreign body (a T tube, 17 cm. in length) remained in the duodenum for years without causing symptoms.[4]

Ninety-five cases of perforation of the intestine by ingested bodies reported by a number of authors were reviewed in a study in 1941.[5] Only 18 per cent of the patients were in the first decade of life, and in only a single instance did a patient have knowledge of ingestion of the foreign body. While the cardioesophageal junction, the pylorus and the duodenum provide relatively fixed points and narrowed passageways, the preponderance of perforations was in the lower ileac and cecal regions. Only 5 of the perforations were in the gastroduodenojejunal areas. In 5 cases of acute perforation of the intestine by ingested fishbones, it was noted that abscesses may be far removed from the site of perforation and that fatal blood stream infection may follow perforation of a vein by the bone.[6]

Attention has been directed to the reasons for the tendency of long, slender objects to lodge in the duodenum.[7] The major portion of the duodenum is

From the Department of Pediatrics, Carle Memorial Hospital.

1. Henderson, F. F., and Gaston, E. A.: Ingested Foreign Body in the Gastro-Intestinal Tract, Arch. Surg. **36**:66 (Jan.) 1938.

2. Delaney, C. J.: Foreign Bodies Swallowed by Children, New York State J. Med. **40**:1024 (July 1) 1940.

3. Van Loon, E. L., and Diamond, S.: Foreign Bodies in the Gastrointestinal Tract, Ann. Otol., Rhin. & Laryng. **51**:1077 (Dec.) 1942.

4. Brown, T. P., and Crew, R. S.: An Unusual Case of Duodenal Foreign Body, J. A. M. A. **115**:125 (July 13) 1940.

5. Macmanus, J. E.: Perforation of the Intestines by Ingested Foreign Bodies, Am. J. Surg. **53**:393 (Sept.) 1941.

6. Bunch, G. H.; Burnside, A. F., and Brannon, L. J.: Intestinal Perforation from Ingested Fishbone, Am. J. Surg. **55**:169 (Jan.) 1942.

7. Silvernale, F. P.: Foreign Body (Bobbie Pin) in the Duodenum, Journal-Lancet **59**:190 (May) 1939.

retroperitoneal and relatively immobile; it is a rigid tunnel with deep transverse rugae which tend to impede the passage of any object. The relatively narrow lumen of the child's duodenum adds to the difficulty of a long object's successfully negotiating the turns of this first portion of the intestinal tract.

Bobby pins when swallowed by children may cause difficulty because the length of these metal bodies is conducive to duodenal lodgment. Several authors reported bobby pins caught in the third portion of the duodenum, with successful removal after laparotomy through a small incision in the duodenum.[8] In another case, removal was by duodenoscope, through a gastrostomy opening.[9] Urinary disturbances due to perforation by an ingested foreign body, one in the duodenum and another through the bowel, with the object lying parallel to the prostatic urethra, were reported.[10] The foreign body in one of the cases was a bobby pin.

From reports in the literature and from my own experience it is apparent that lodgment of ingested foreign bodies in the duodenum with subsequent perforation is uncommon in both children and adults. I am reporting an unusual case of perforation of the duodenum by a bobby pin with associated symptoms suggesting disease of the hip. In this child the foreign body had broken in two pieces, each of which perforated the intestinal wall some two and one-half months prior to surgical removal. The usually benign status of foreign bodies in the intestinal tract is illustrated in the brief report on 3 other patients, all younger than the first, who passed ingested bobby pins uneventfully. All the reported patients were seen within a period of a few months.

REPORT OF CASES

CASE 1.—J. H., a girl 24 months of age, was first seen at the clinic April 6, 1948, with a complaint of pain in the right hip and a pronounced limp. The father and mother were alive and well, and the family history was essentially irrelevant. She had been delivered at term, and the birth history was normal. The past medical history was noncontributory and the developmental history normal.

About February 1, she had had a cold and was treated with one of the sulfonamides. At the same time, she complained of pain in the area of the right hip and refused to bear weight on the right leg. Because of persistent pain, roentgenographic studies of the hip were made elsewhere on February 14; nothing abnormal about the hip was noted on the films. However, on these roentgenograms it was observed that the child had a "broken bobbie pin" in her "intestinal tract." Since there was no history of ingestion of a foreign body, it was impossible to determine when the incident had occurred. The child's condition remained unchanged, and on April 5 further roentgenographic studies of the hip were made elsewhere; the bobby pin was again noted, but nothing abnormal in the hip was evident. Because of the persistent limp and the complaint of pain in the right hip, she was brought to the clinic.

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8. (*a*) Faber, J.: Haarspangen im Duodenum, Chirurg. **13**:286 (May 1) 1941. (*b*) McEnery, E. T., and Fox, P. F.: Foreign Body in the Duodenum Causing Urinary Disturbance, J. Pediat. **29**:226 (Aug.) 1946.

9. Latraverse, V., and Ricard, P.: Duodenoscopic Removal of a Bobbie Pin Through a Gastrostomy in a Child Thirteen Months Old, Canad. M. A. J. **51**:560 (Dec.) 1944.

10. McEnery and Fox.[8b] McKechnie, W. R.: Perforation of Intestine by Ingested Sharp Foreign Body, Australian & New Zealand J. Surg. **13**:265 (April) 1944.

Physical examination on April 6 showed a well nourished, frightened girl who did not appear acutely ill. Examination was difficult because of her irritability. Her weight was 11.4 Kg. The rectal temperature was 37.2 C. (99 F.). The tonsils were moderately enlarged and fibrotic. The heart, lungs, abdomen and genitals were normal. She walked with a slight limp on the right, but in the supine position there seemed to be no limitation of motion at the right hip or knee. Neurologic examination revealed no abnormality.

Fig. 1.—Two pieces of bobby pin in the right midabdomen. They remained in this same position for two weeks.

Urinalysis showed a specific gravity of 1.018, negative reactions for albumin and sugar and normal microscopic appearance. The blood count showed a hemoglobin concentration of 11.1 Gm., or 71 per cent, 3,880,000 erythrocytes and 15,400 leukocytes, with 30 per cent neutrophils and 70 per cent lymphocytes. The Vollmer tuberculin test and the blood Kline and Kahn tests gave negative reactions. The sedimentation rate (Smith) was 3 mm. in fifteen minutes and 17 mm. in forty-five minutes. Roentgenographic studies of both hips and knees and the chest showed no

abnormality. Roentgenologic studies of the abdomen disclosed two pieces of a broken bobby pin in the right midportion, and these were thought to be in the colon. Because of the leukocytosis and the presence of the foreign body in the bowel, it was decided to reexamine the child in a week.

On April 15, she was seen again. The leukocyte count at that time was 10,500. On this visit she neither limped nor complained of the hip. Roentgenograms of

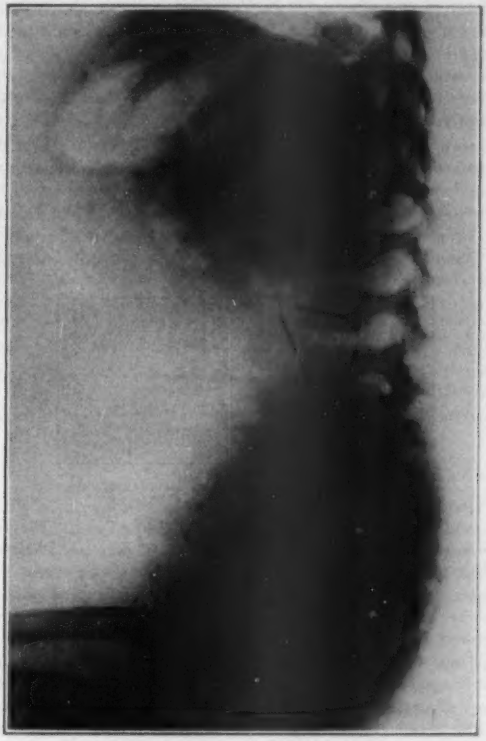

Fig. 2.—Lateral view of the two pieces of bobby pin.

the abdomen at this visit were interpreted as showing the two metallic bodies outside the colon, probably within the psoas muscle. The outline of the right psoas was obliterated (see fig. 1). Surgical consultation was requested, and it was decided to explore the right psoas area.

With the patient under anesthesia induced by vinyl ether (vinethene®) and ether, laparotomy was performed on April 21. Just prior to anesthetization, roentgenographic studies showed that the position of the foreign bodies had not changed. Through a right rectus incision from the level of the midepigastrium to a point

4 cm. below the umbilicus, the right psoas muscle was examined. In the horizontal portion of the third part of the duodenum a firm, thin object was palpated. This portion of the duodenum was carefully brought into view and mobilized with some difficulty because of its adherence to the psoas muscle by a strand of indurated tissue. The indurated area was isolated and opened to remove a portion of bobby pin, 4 cm. in length, which had perforated the lower part of the duodenum. The foreign body was partially within the lumen of the bowel, with the perforating point embedded in a granuloma of the psoas muscle. The second foreign body, 2.5 cm. in length and located 1.5 cm. from the first, also perforated the bowel and was embedded in the granuloma. It was similarly removed. Following this, the perforations were closed transversely and the abdomen was closed. Dextrose in isotonic sodium chloride solution and a transfusion of blood were given during the surgical procedure. Figure 3 illustrates the findings at laparotomy.

The course for the first three days after surgical intervention was moderately stormy. Intravenous infusions were given daily, and sulfadiazine sodium and penicillin were given parenterally. On April 24, her general condition was good, the abdomen was soft and the bowel sounds were normal. The administration of sulfadiazine sodium was discontinued, and another transfusion of whole blood was given. On April 28, urinalysis showed a specific gravity of 1.022, an alkaline

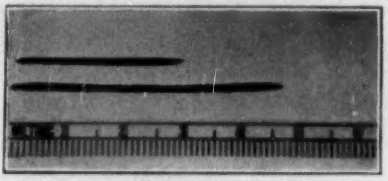

Fig. 3.—Pieces of bobby pin after removal.

reaction, a faint trace of albumin and 15 to 20 red blood cells. The blood count showed a hemoglobin concentration of 16.8 Gm., or 107 per cent, 5,580,000 erythrocytes and 14,500 leukocytes, with 51 per cent neutrophils, 48 per cent lymphocytes and 1 per cent eosinophils. She was dismissed from the hospital on April 29, at which time she had been completely afebrile for three days. Her condition at dismissal seemed good.

She was well for several days at home, but on the evening of May 1 she vomited and complained of her abdomen, and on May 2 she was readmitted to the hospital. Her temperature (rectum) was 38.6 C. (101.5 F.), and she was moderately toxic and dehydrated. The abdomen was slightly distended. The blood count showed 15.9 Gm., or 102 per cent, of hemoglobin, and 5,520,000 erythrocytes, 11,800 leukocytes, with 45 per cent neutrophils and 55 per cent lymphocytes. Urinalysis revealed no abnormality. Roentgenographic studies of the abdomen showed distention of the intestinal loops on the left with multiple fluid levels. Neostigmine (prostigmin®) methylsulfate was given at three hour intervals for six doses without apparent change in the obstruction, and administration of penicillin and fluids intravenously was started. On May 4 a Miller-Abbott tube was passed under fluoroscopy and the tip, after several hours, was reported in the duodenum. On May 5 the serum protein was 5.2 Gm. and the chlorides were 700 mg. per hundred cubic centimeters. The abdomen was soft, and the tube drained

greenish fluid. On May 6 the tip of the tube was located in the ileum and satisfactory decompression had been accomplished. No flatus had been passed since her admission to the hospital.

Surgical exploration for relief of the obstruction was done that same day. At a point 30 cm. above the cecum, a thick adhesion fixed the small bowel to the base of the mesentery. This was released. Three centimeters of serosa in the region had split and this defect was sutured. The bowel proximal to this point was distended and flaccid due to the obstruction. The region of the third portion of the duodenum, the site of the previous surgical procedure, was examined and no masses or unusual induration was observed.

The postoperative course was uneventful, and no vomiting occurred after surgical treatment. By May 11 the patient was afebrile and was passing greenish stools. On May 13 the blood count and urine were normal, and she was dismissed from the hospital. Her condition since dismissal has been excellent.

Case 2.—R. R., a girl 22 months of age, swallowed a bobby pin on Sept. 4, 1948. She choked for a moment and then had no further symptoms. Roentgenographic studies showed a bobby pin measuring 4.7 cm. in the stomach. On September 6 the pin was located in the duodenum, and on September 7 it was passed.

Case 3.—M. W., a girl 22 months of age, swallowed a bobby pin on Aug. 17, 1948. She did not choke, and there were no symptoms. A roentgenogram showed the foreign body in the stomach. On August 20 roentgenologic studies showed the pin had been passed, although it was not recovered.

Case 4.—C. E., a girl 16 months of age, swallowed a bobby pin on Oct. 28, 1948. She choked for a moment, and there were no further symptoms. A roentgenogram of the abdomen on October 28 showed the foreign body in the stomach; another film on October 30 showed the body in the upper portion of the small bowel. It was passed on October 31.

COMMENT

The symptoms from perforating foreign bodies in the intestinal tract are usually sharp, constant and severe abdominal pain or more gradual abdominal pain, with low grade fever, anorexia and localized tenderness. The complaints in case 1 of limp and pain in the hip due to the indurated, inflammatory area in the psoas region have not been previously reported. An occurrence of bizarre symptoms in a patient with a sharp or elongated foreign body lodged in a portion of the intestinal tract should suggest the possibility of perforation.

A program of watchful waiting and frequent careful observation by x-ray and fluoroscope, rather than a precipitate operation for a foreign body in the stomach, has been proposed.[11] This would coincide with my opinion, since even relatively long bodies usually pass through the intestinal tract of young children spontaneously. As a prophylactic measure, all elongated foreign bodies in the stomach, the passage of which through the intestine might involve risk, could be removed through the mouth by gastroscope. Unfortunately, persons skilled in such services are often not available. Should a foreign body remain in one location referable to a viscus for as long as a week, prompt abdominal section for removal is indicated.

602 West University Avenue.

11. Delaney,[2] Moreau, M. H., and Noguera, O. F.: Ingestión de cuerpos extraños: Consideraciones clínio-radiologicas, Semana méd. **1**:1318 (April 26) 1934.

AURICULAR FLUTTER IN INFANCY

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AND
STANLEY GIBSON, M.D.
CHICAGO

Auricular flutter in infancy and childhood is rare. A search of the literature has revealed only 12 well authenticated cases. Of these, 6 occurred in infants under 1 year of age. Excellent clinical summaries of these cases have been given by Prince and Rotondo [1] and by Hoyer and Lyon.[2]

The case herein reported not only adds to the small number of cases previously described but presents some unusual features which we believe make it worthy of being placed on record.

REPORT OF A CASE

R. H., a 6 month old white boy, was admitted to the Children's Memorial Hospital on May 11, 1949 because of "heart trouble since birth." The child was born three weeks prematurely. Delivery was normal. The weight at birth was 5 pounds 13 ounces (2,637 Gm.). The mother had been well during her pregnancy.

Intense cyanosis and dyspnea were present at the time of birth. The obstetrician's note described "asphyxia livida with a respiratory rate of eighty per minute." A roentgenogram of the chest taken shortly after birth showed definite cardiac enlargement and questionable atelectasis. The cyanosis and dyspnea improved slowly, and at the time of his discharge from the hospital on the twelfth day both were minimal. However, another roentgenogram of the chest taken at that time revealed a decidedly enlarged globular heart, but there were no remaining signs of atelectasis. On one occasion during the stay in the hospital, the resident was of the belief that he heard a soft systolic murmur to the left of the sternum. After his discharge from the hospital, the baby was seen regularly by a competent pediatrician, who noted in his check-up at the age of 3 months that the heart was enlarged. The rate was regular and no murmur was heard. The general condition was excellent. On examination at the age of 4 months, the cardiac rhythm was irregular, the breathing was rapid and the liver was enlarged.

There was a history of frequent infections of the upper respiratory tract, though the baby had gained weight normally. The family history was noncontributory.

Physical examination at the time of his admission to the hospital revealed a well developed and well nourished 6 month old white boy, weighing 16 pounds 9 ounces (7,413 Gm.). The breathing was somewhat rapid but not labored. The baby was active and his color was excellent. The pulmonary fields were clear. The cardiac apex was felt in the fifth interspace just outside the nipple line. There

From the Children's Memorial Hospital.

1. Prince, G. E., and Rotondo, C. C.: Auricular Flutter and Congenital Heart Disease, Am. J. Dis. Child. **72**:552-562 (Nov.) 1946.

2. Hoyer, B., and Lyon, R. A.: Auricular Flutter with Block in Children, Am. J. Dis. Child. **72**:734-742 (Dec.) 1946.

was definite cardiac enlargement on percussion of the heart borders. No murmur was heard. The heart rate varied from 100 to 180 and was grossly irregular. On careful and prolonged auscultation one could occasionally hear short runs of what seemed to be a perfectly regular rhythm.

Fluoroscopic examination in the anteroposterior view showed normal vascular markings, enlargement of the heart to the right and a wide mediastinal shadow. In the left anterior oblique view, there was definite enlargement of the right auricular appendage and of the inflow tract of the right ventricle. In the right

Fig. 1.—Lead I, auricular flutter with varying conduction, ratio changing from 2:1 to 6:1.

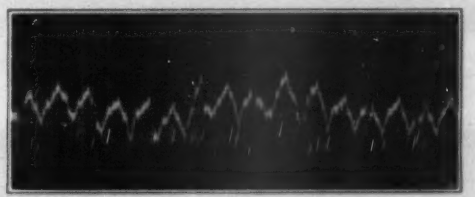

Fig. 2.—Lead II, auricular flutter showing early quinidine effect. Conduction varies from 2:1 to 3:1, with a slowing of the auricular rate to approximately one-half the original. The different amplitude and direction of the QRS complexes also show quinidine effect.

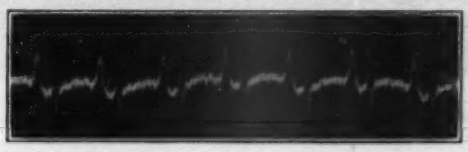

Fig. 3.—Lead II, temporary conversion to normal sinus rhythm. Note the tall and peaked P waves.

anterior oblique view enlargement of the body of the right auricle and of the outflow tract and conus portion of the right ventricle was seen.

An electrocardiogram taken on May 13, 1949 showed an average ventricular rate of 150 and an auricular rate of 500. The degree of auriculoventricular block varied from 3:1 to 5:1. Occasionally, the flutter was impure. There was also evidence of strain on the right side of the heart, and the tracing was reported as being "definitely compatible with congenital heart disease."

In an attempt to restore normal rhythm 1 grain (0.06 Gm.) of digitalis U. S. P. was given as an initial dose, followed by ¼ grain (15 mg.) every six hours for four doses. The drug was poorly tolerated. The child became listless, the respira-

tory rate was increased and all food was refused. The rhythm became irregular and the rate varied from 60 to 180. Treatment with digitalis was discontinued, and within thirty-six hours the child appeared as he had on admission.

It was then decided to use quinidine sulfate U. S. P. To prevent the possibility of speeding up the ventricular rate, the baby was first given a small daily dose of digitalis (0.2 grain [12 mg.]) then 0.3 grain (18 mg.) of quinidine sulfate was administered as a test dose. Inasmuch as there were no signs of sensitivity to quinidine, as indicated by vomiting, flushing of the skin, rash, irritability or depression, 0.6 grain (36 mg.) was given every two hours for five doses. Electrocardiograms taken every two hours during that day showed an interesting and gradual change from auricular flutter to an impure flutter, then to auricular

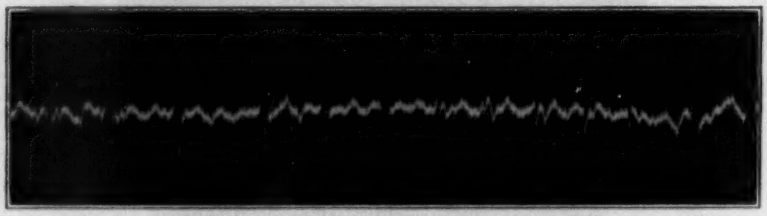

Fig. 4.—Lead I, toxic effect of quinidine. Note the small, prolonged and notched QRS complexes secondary to quinidine toxicity.

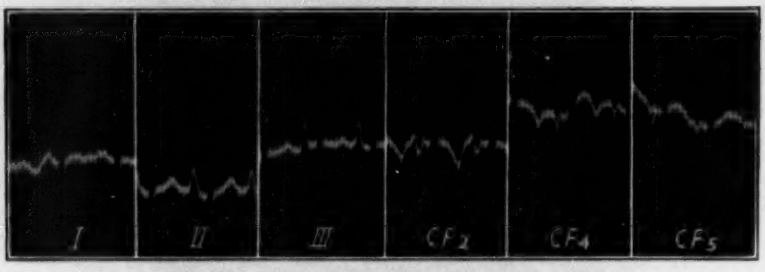

Fig. 5.—Final follow-up electrocardiogram showing sinus mechanism. Pulse rate was 140; PR interval measured 0.18 second. Note strain on the right side of heart as indicated by Wilson's phenomenon in the chest leads.

fibrillation and, finally, to a normal sinus rhythm. At that time a soft systolic murmur could be heard in the second and third left interspaces near the sternum.

On return to sinus mechanism the amount of quinidine given was reduced to 0.3 grain every six hours as a maintenance dose. However, on examination of the patient on the following morning the irregular rate was again present, and the electrocardiogram showed a complete return to the original pattern of auricular flutter, with associated auriculoventricular block. Quinidine sulfate was again tried in a dosage of 0.6 grain (36 mg.) every two hours for five doses, but this time with no effect. The dose was then increased to 0.9 grain (54 mg.) every two hours. After the third dose the pulse became extremely irregular. The patient refused all food and became lethargic. The electrocardiogram showed a serious auriculoventricular block, and it was felt that the use of quinidine should

be stopped. Within twenty-four hours the child's condition improved, and an electrocardiogram made at this time was similar to that on admission, save that the ventricular rate was somewhat slower. The patient was discharged from the hospital on June 1, 1949, and a daily dose of 0.2 grain of digitalis was prescribed.

He was not seen again until July 28, 1949. The baby had been happy, had taken his feedings well and had made an excellent gain in weight. At this time the heart seemed perfectly regular and an electrocardiogram revealed normal sinus rhythm. The cardiac enlargement was still present. No murmur was heard.

COMMENT

It is well known that auricular flutter occurs in the course of organic heart disease, as a complication of acute infections and in instances in which no evidence of organic disease is present in the heart or elsewhere. In the present case we believe that there is well-nigh indisputable evidence of congenital heart disease. The cardiac enlargement limited chiefly to the right chambers, the tall and peaked P waves in leads II and III and the strain on the right side of the heart in an infant 6 months of age would be difficult to explain on any other basis. Moreover, the observations suggest that the lesion is probably a defect of the auricular septum. Not only are the physical signs, results of fluoroscopic examination and electrocardiogram compatible with this diagnosis, but it has been emphasized by Taussig [3] and others that arrhythmias, including auricular flutter, are especially likely to occur in defects of the auricular septum.

In the treatment of auricular flutter in infants the same principles have been employed that have proved helpful in older persons. Digitalis is usually the drug of choice and its use should be pushed to the point of full physiologic action with an adequate maintenance dose. If this fails to restore normal rhythm, treatment with quinidine should be given a trial. Use of digitalis should be continued during the administration of quinidine to avoid the possibility of a 1 : 1 flutter as the auricles slow down. The dosages of digitalis and quinidine which we used were computed in accordance with the baby's weight as compared with that of an adult.

In our patient we failed to achieve immediate success with administration of either drug. Whether the later return to normal mechanism resulted from the continued daily administration of digitalis or whether the conversion was purely spontaneous we are unable to say.

SUMMARY

A case of auricular flutter in a 6 month old white boy is reported.

Administration of digitalis and quinidine resulted in a temporary return to sinus mechanism but could not be maintained on doses as large as safety would permit.

Two and a half months later the patient was found to have normal sinus rhythm. During this period he had been receiving 0.2 grain (12 mg.) of digitalis daily.

The patient has signs indicating the presence of congenital heart disease, probably a defect of the auricular septum.

707 West Fullerton Avenue (14).

Dr. John S. McDavid permitted us to report this case. Dr. Jakub Schlichter interpreted the electrocardiograms.

3. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947.

INFANTILE CORTICAL HYPEROSTOSIS

Report of a Case with Observations at Autopsy

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DENVER

"All science suffers from the vice that it may be combining various propositions which tacitly presuppose inconsistent backgrounds. No science can be more secure than the unconscious metaphysics which tacitly it presupposes. . . . Thus the certainties of science are a delusion. They are hedged around with unexplored limitations."

—Alfred North Whitehead.

Roentgenographic studies, initiated by Roske (1930)[1] and augmented by many others, including Caffey (1939; 1945; 1946)[2] and Smyth, Potter and Silverman (1946),[3] have resulted in the clinical description of a syndrome now known as "infantile cortical hyperostosis."[4]

Dr. Harry Gordon and Dr. Elaine Fichter provided clinical data for this paper.

From the Child Research Council and the University of Colorado School of Medicine, Department of Pathology.

1. Roske, G.: Eine eigenartige Knochenerkrankung im Säuglingsalter, Monatsschr. f. Kinderh. **47**:385, 1930.

2. (*a*) Caffey, J.: Syphilis of the Skeleton in Early Infancy: The Nonspecificity of Many of the Roentgenographic Changes, Am. J. Roentgenol. **42**:637, 1939. (*b*) Caffey, J., and Silverman, W. A.: Infantile Cortical Hyperostosis: Preliminary Report on a New Syndrome, ibid. **54**:1, 1945. (*c*) Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery & Radiology, Chicago, The Year Book Publishers, Inc., 1945, p. 774, fig. 675; (*d*) Infantile Cortical Hyperostosis, J. Pediat. **29**:541, 1946.

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4. (*a*) Dickson, D.; Luckey, C. A., and Logan, N. H.: Infantile Cortical Hyperostosis, J. Bone & Joint Surg. **29**:224, 1947. (*b*) Whipple, R. K.: Infantile Cortical Hyperostosis, New England J. Med. **236**:239, 1947. (*c*) Kane, S. H., and Borzell, F. F.: Infantile Cortical Hyperostosis, Am. J. Roentgenol. **58**:629, 1947. (*d*) Delano, P. J., and Butler, C. D.: The Etiology of Infantile Cortical Hyperostosis, ibid. **58**:633, 1947. (*e*) Fisk, C.: Infantile Cortical Hyperostosis, J. Iowa M. Soc. **37**:529, 1947. (*f*) Shuman, H. H.: Infantile Cortical Hyperostosis, J. Pediat. **32**:195, 1948. (*g*) Gipson, A. C., and Clark, B. P.: Infantile Cortical Hyperostosis, Pediatrics **1**:221, 1948. (*h*) Burke, F., in Conference on Infantile Cortical Hyperostosis (Caffey-Smyth Syndrome), J. Pediat. **32**:441, 1948. (*i*) Ross, S.; Burke, F. G.; McLendon, P. A., and Spencer, H.: Caffey-Smyth Syndrome: A Report of Ten Cases, to be published. (*j*) Chen, K. T., and Yu, T. S.: Infantile Cortical Hyperostosis: Report of a Case, Chinese M. J. **66**:266, 1948. (*k*) Thompson, C. G.: A Case of Infantile Cortical Hyperostosis (Caffey-Smyth Syndrome), Connecticut M. J. **13**:22, 1949. (*l*) Bauman, C. S.,

This malady has an abrupt onset and runs the initial part of its course during the first few months of infancy. Acute manifestations—fever, anemia, lymphocytosis, increased sedimentation rate of erythrocytes and tender brawny nonhyperemic edema of soft tissues overlying affected bone—subside spontaneously after a few weeks. Roentgenograms of the skeleton made during this period show scattered focal periosteal "reactions," with lamellated thickening of various bones, including the mandible, scapulas, ribs, femurs, tibias and fibulas. Although self limited, the disease is protracted for several months and terminates gradually, with roentgenologic evidence of slow retrogression of osseous changes until involved bones regain their normal contours.

Attempts to determine etiologic factors and to obtain therapeutic responses have been disappointing.[5]

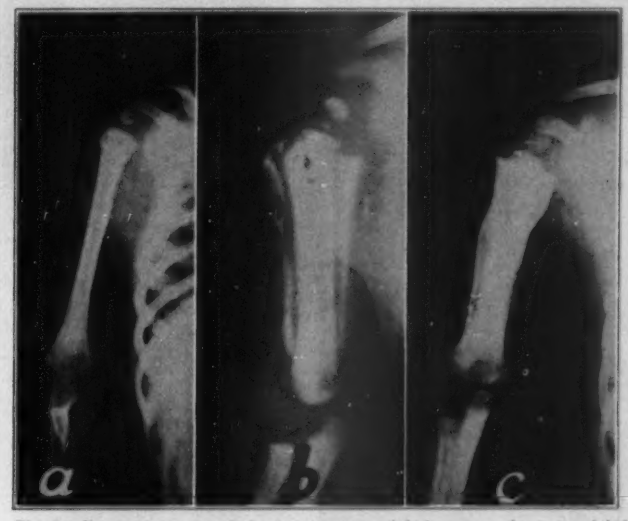

Fig. 1.—Roentgenograms of the humerus: *a*, left humerus of a normal baby 5½ months of age. This photograph is shown to compare with *b* and *c*. *b*, left humerus of patient, one month ante mortem. *c*, left humerus of patient, post mortem.

Because all the children with this syndrome heretofore observed have apparently recovered, it may be considered profitable to present the case of an infant who died, fortuitously perhaps, during the course of his illness.

REPORT OF CASE

Clinical Summary.—A white baby boy 5½ months of age was admitted to the Colorado General Hospital, Nov. 16, 1947, with painful enlargement of both arms and blue-black discolorations of the skin. According to the mother, the infant had

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and Lubell, M. F.: Infantile Cortical Hyperostoses, J. Maine M. A. **40**:5, 1949. (*m*) O'Reilly, J. N.: Infantile Cortical Hyperostosis, Arch. Dis. Childhood **24**:67, 1949. (*n*) Sherman, M. S.: Infantile Cortical Hyperostosis, Proc. Inst. Med. Chicago **12**:307, 1949. (*o*) Berkheiser, E.: Caffey's Disease, ibid. **12**:308, 1949.

5. Caffey.[2d] Smyth and others.[5] Footnote 4*d*, *f*, *h* and *i*.

daily received fresh orange juice, 50 mg. of ascorbic acid and 8 drops of percomorph liver oil. His illness began quite abruptly six weeks before as a painful swelling of the right shoulder and arm. For ten days he was in another hospital and treated

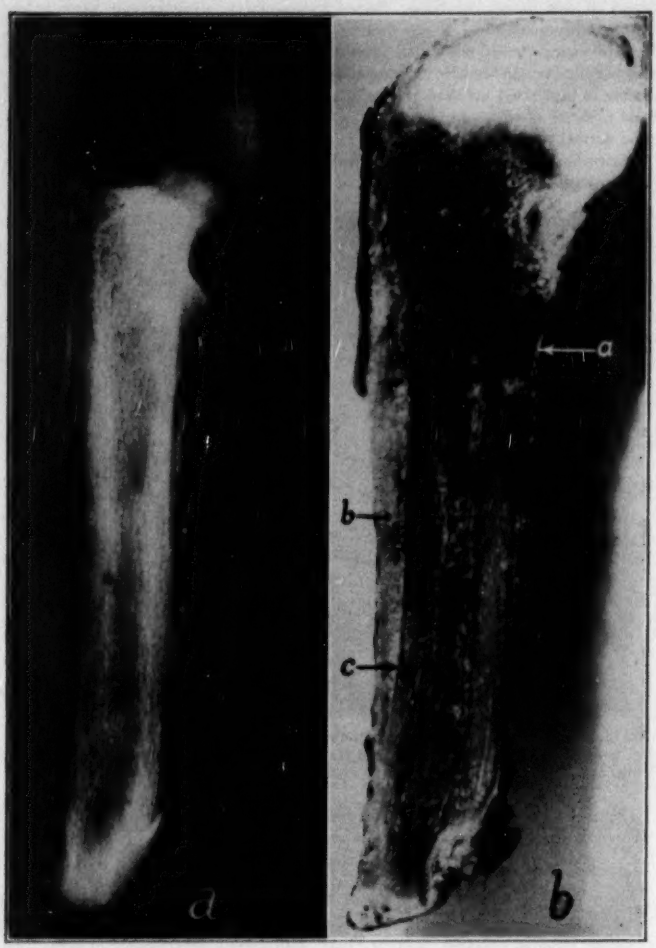

Fig. 2.—(*a*) roentgenogram of the left humerus after it had been removed and sectioned longitudinally: *a* is excess bone and *b* original surface of humerus. (*b*) photograph of the left humerus sectioned longitudinally: *a* indicates thick periosteum, *b*, excess bone, and *c*, original surface of humerus.

for scurvy. Edema of the right arm persisted, subsiding and recurring at one or two week intervals in spite of antiscorbutic therapy. On November 15 the left arm became tender and swollen.

The patient was well developed and nourished and appeared comfortable until his arms were moved. There were small palpebral and conjunctival hemorrhages, as well as several ecchymoses of the skin, 1 to 4 cm. in diameter, on the head and thorax. Inguinal and axillary lymph nodes were discrete, firm and slightly enlarged. The skin of both arms and elbows was brawny, although normal in appearance. Palpation suggested great thickening of both humeri. The forearms, legs and thighs presented no abnormality. The rectal temperature was 102 F. Descriptions of the roentgenograms of the humeri contained such terms as "cortical

Fig. 3.—Photograph of left humeral head sectioned longitudinally: *a* indicates the ossification center, and *b* marks the rough epiphysial line.

thickening" and "increased calcification" (fig. 1*b*). Serologic tests for syphilis and tuberculin skin tests gave negative reactions. Various blood examinations showed 17,000 to 24,000 white blood cells per cubic millimeter, with lymphocytic predominance; an average red blood cell count of 3,600,000; an average thrombocyte count of 130,000, and normal bleeding, clotting, retraction and prothrombin times. Acid phosphatase measured, 2.9 Bodansky units; alkaline phosphatase, 6.9 units; serum calcium, 8.9 mg., and serum phosphorus, 5.4 to 6.3 mg. per hundred cubic centimeters. Gram-positive encapsulated diplococci resembling pneumococci were cultured from material in the throat.

The child improved without particular treatment during his stay in the hospital. Tenderness of the elbows and the cutaneous hemorrhage disappeared. The arms, however, remained enlarged. A biopsy specimen of the left humeral diaphysis showed newly formed cancellous bone, with moderately vascularized connective tissue filling the haversian spaces. During the last week of his hospitalization the patient was afebrile, cheerful, eating well and gaining weight. On December 8, he was discharged to his parents, who were instructed to return their child for occasional observation. They brought their baby back with the story that he had appeared well until the morning of Jan. 30, 1948, when they found him dead in bed.

Fig. 4.—Photomicrograph of epiphysial line of the left humerus: *a*, connective tissue strand running from diaphysis into epiphysis; *b*, disruption of adjacent lacunar palisades.

Autopsy Observations.—The infant's body had been embalmed. Irregular sepia-red ecchymotic spots, 5 to 10 mm. in diameter, were scattered throughout the skin of the trunk and extremities. The thymus, weighing 25 Gm., was pale red and normal in shape, position, consistency and cut surface markings. The moderately firm spleen, weighing 22 Gm., showed flat cut surfaces with distinct lymphoid nodules. The hyperemic and edematous mesentery was studded with large violescent lymph nodes. Peyer's patches of the ileum were prominent and intensely injected, and each presented a small central focus of mucosal necrosis. Postmortem roent-

genograms of the entire skeleton showed "cortical thickening" and "hyperostotic lipping" of some of the long bones, particularly the femurs and humeri (figs. 1*c* and 2*a*). On section the surface of the left humerus, sawed through its longitudinal axis, exhibited pronounced thickening of the "cortex," narrowing of the medullary

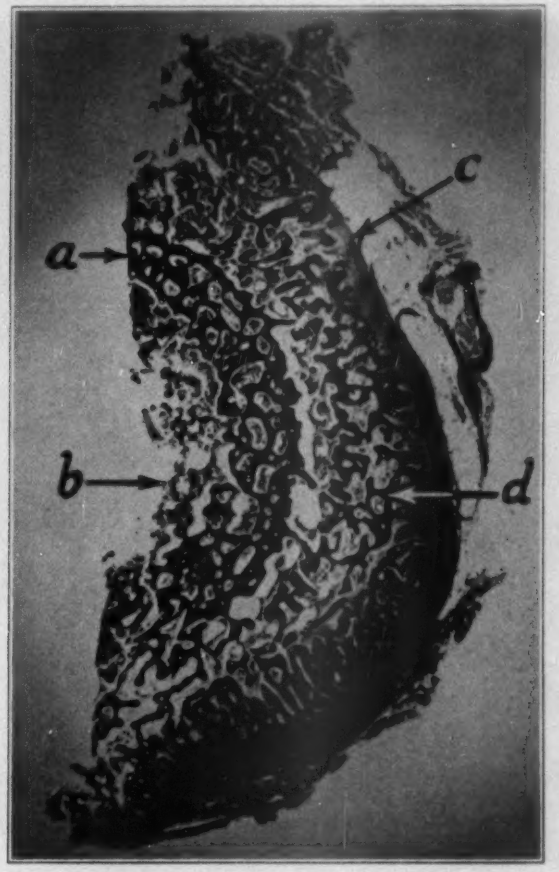

Fig. 5.—Photomicrograph of transverse hemisection of left humeral diaphysis (hematoxylin and eosin stain; × 4.8): *a*, inner layer of cancellous bone; *b*, medullary cavity; *c*, thick periosteum, and *d*, outer shell of spongy bone.

cavity and some roughening of the epiphysial line (figs. 2*b* and 3). Just beneath the thick periosteum was a 3 mm. layer of cancellous bone which appeared like a cylindric investment of the humeral diaphysis. Immediately beneath this appeared another layer of spongy bone, the outer margins of which were straight, followed

the contours of a normal humerus and seemed to represent the original shaft of the bone (figs. 2*b* and 5). The humeral head contained one ossification center (fig. 3). Hemorrhages or foci of necrosis were not observed.

Other organs, including the parathyroid glands, were not remarkable.

Fig. 6.—Photomicrograph of inner layer of cancellous bone (hematoxylin and eosin stain; × 60): *a*, section through trabeculae; b, incomplete layer of osteoblasts, and *c*, bone marrow in haversian spaces.

Microscopic Examination.—Follicular germinal centers and sinuses of mesenteric and parabronchial lymph nodes were "active appearing" and filled with large pale-stained mononuclear cells, some of which had ingested lymphocytes. Sinusoids

of the spleen contained much blood and brown pigment. Splenic nodules, huge and numerous, were centrally packed with large mononucleated cells with clear cytoplasm. Peyer's patches showed vascular congestion, edema, lymphoid hyperplasia, central erosion of covering epithelium and focal hemorrhage of subepithelial tissue, with localized infiltration of polymorphonuclear leukocytes.

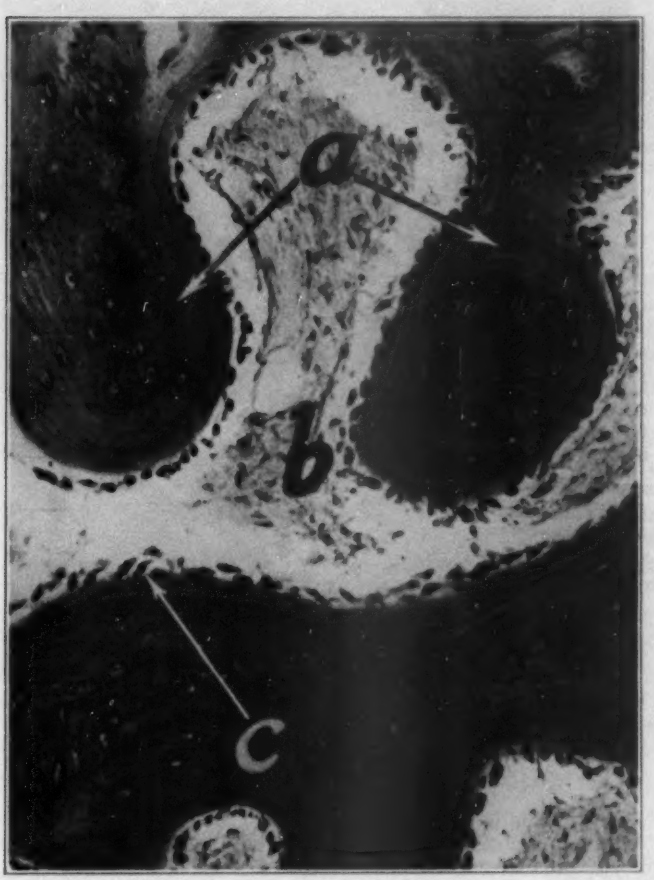

Fig. 7.—Photomicrograph of outer layer of cancellous bone (hematoxylin and eosin stain; × 60): *a*, sections through trabeculae; *b*, connective tissue in haversian spaces, and *c*, complete layer of osteoblasts.

In the humerus the epiphysial line of ossification was interrupted in places by strands of connective tissue, containing trabeculae of cartilage and bone, running from the diaphysis into epiphysial cartilage (fig. 4). These strands altered the

lacunar arrangement in the epiphysial line only in regions immediately adjacent to them. Compact bone was observed nowhere in the sections. Spongy bone appeared in two rather distinct layers (fig. 5), the inner one of which contained marrow cells in its haversian spaces and a few haversian patterns in the bone itself. The

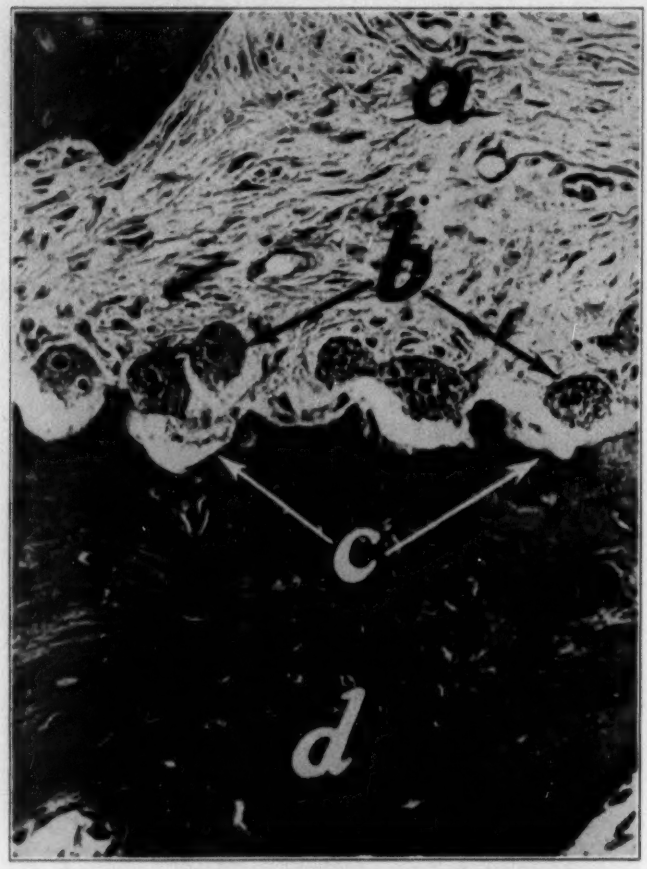

Fig. 8.—Photomicrograph of the osteoperiosteal apposition (hematoxylin and eosin stain; × 80): *a*, periosteum; *b*, osteoclasts; *c*, Howship's lacunas, and *d*, trabecula of bone.

trabeculae seemed to have had a recent deposition of new bone which was sharply delineated from the older, more calcified and darkly stained bone. These trabeculae were scantily clad in a single incomplete layer of osteoblasts (fig. 6). The outer layer of cancellous bone contained only mildly vascularized loose fibrillary tissue

in its haversian spaces and showed less of the haversian pattern in the trabeculae, which were completely covered with a layer of osteoblasts (fig. 7). Immediately beneath the periosteum, which was remarkably thickened with fibrocytes and collagen fibrils, the bone was scalloped into Howship's lacunas, in each of which lay a multinucleated osteoclast (fig. 8). Evidence of inflammation was not observed. Levaditi slide preparations showed no Treponema pallidum.

COMMENT

The bone lesions of this infant may represent the basis of a syndromic entity. That there is a relationship between the ileitis and generalized lymphoid hyperplasia and skeletal disease is, however, quite conjectural. There was not enough involvement of the lungs to presuppose pulmonogenic hypoxemia as the death-dealing process. If acute cerebral anoxia occurred, it was not of sufficient duration to produce demonstrable morphologic changes in neuronal bodies of the cerebrum, cerebellum, midbrain or medulla oblongata.[6] Enteritis, unless it was due to some unknown especially virulent infectious agent, certainly cannot account for the fatality. However, it must be admitted that the histologic aspects of lymph nodes and Peyer's patches suggest typhoid.[7] Morphologic changes reveal nothing of the pathophysiologic processes which produced them. Acceleration of osteogenesis was confined only to its periosteal components. As a result, the length of the long bones was not increased. Indeed, comparison with normal bones of the same age suggests that epiphysial function may have been decelerated, with resulting shorter bones than normal. Possibly excessive vitamin A, speculatively admissible as a factor in this case, upset the metabolic balances enough to retard bony linear growth and to accelerate periosteal activity.[8] Pain in the arms and sleeplessness could have been due to stretching and irritation of sensory end organs in the periosteum. Lymphoid hyperplasia and lymphocytosis may have been compensatory for decreased hemopoiesis in the bone marrow and anemia.

Inasmuch as a delicate balance exists between bone formation and bone stabilization or destruction—the former gaining ascendency during the growth period, the latter during senescence—it could be that an infectious process, pharyngitis or enteritis, disturbed the baby's metabolic processes sufficiently to produce bone changes without altering the chemical composition of the blood.[9] Because all structures formed by the connective tissue groups arise from mesenchymal cells, and in view of their closely related functions, common ancestry and facility for

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7. Moore, R. A.: A Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944, pp. 353-358. Breck, M. R., and Mossberger, J. I.: Infantile Typhoid with Convulsions, J. A. M. A. **119**:25 (May 2) 1942.

8. Rothman, P. E., and Leon, E. E.: Hypervitaminosis A: Report of Two Cases in Infants, Radiology **51**:368, 1948.

9. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, pp. 700-721. Kolmer, J. A.: Clinical Diagnosis by Laboratory Examinations, New York, D. Appleton-Century Company, Inc., 1943, pp. 138-142.

adaptation, it may be expected that one connective tissue type will be converted into or replaced by another when a stimulus is imposed or when a need for change occurs.[10]

"Hedged around with unexplored limitations" this case is baffling, and the cause of the child's death remains unknown. Yet, presumptively excluding sudden asphyxia from etiologic considerations, the cause must have been a noxious agent capable of producing symptoms usually attributed to bacteria or to viruses. If the bone lesion of this infant is the result of excessive osteogenesis due to a disturbed metabolic process, initiated by some stimulus of an infectious nature, then its clinical course can be understood. Elimination or neutralization of the causative agent brings about osteoclasis and reversion to normal of the osteogenetic balance.

SUMMARY

A new case of so-called infantile cortical hyperostosis is presented. Lesions observed at necropsy included "cortical thickening" of various bones, generalized lymphadenopathy and, incidentally perhaps, acute focal enteritis. The gross and microscopic appearances of the left humerus are described in detail.

This case of bone disorder in an infant shows most of the morphologic features of excessive embryonal osteogenesis.

4200 East Ninth Avenue (7).

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Progress in Pediatrics

FRIEDLÄNDER-AEROGENES INFECTIONS IN INFANCY

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IN 1882 Friedländer [1] isolated a gram-negative bacillus from the lungs of eight patients and postulated that this organism, which has since borne his name, was the cause of lobar pneumonia. The bacteriologic problem initiated by this discovery was finally resolved in 1886, when Weichselbaum [2] implicated the Diplococcus pneumoniae and relegated the Friedländer bacillus to a less prominent place in the etiology of pneumonia. The latter, however, was still regarded primarily as a pulmonary pathogen.

The publication over the years of isolated case reports of nonpulmonary infection caused by the Friedländer bacillus did not dislodge the prevailing concept that infections induced by this organism were, in the main, respiratory. In 1937 Baehr, Shwartzman and Greenspan [3] reported their experiences with 198 cases of Friedländer infection and challenged this concept by demonstrating a low incidence of respiratory disorders. In only two of their cases did the clinical and bacteriologic studies show unequivocally that they were dealing primarily with Friedländer pneumonia. In seven other cases of lobar and bronchopneumonia the organism was recovered from the sputum or lung in association with other pathogens. In 16 instances it was isolated from the nose and throat in patients with otitis and sinusitis. These authors regarded the Friedländer bacillus largely as an intestinal inhabitant whose usual role in pneumonia is that of a secondary invader.

The material of this report was presented in summary form at the annual meeting of the Louisiana State Medical Society, Baton Rouge, April 26, 1950.

From the Department of Pediatrics, Louisiana State University School of Medicine, and the Pediatric Service, Charity Hospital of Louisiana at New Orleans.

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2. Weichselbaum, A.: Über die Ätiologie der acuten Lungen- und Rippenfellentzündungen, Med. Jahrb. **1**:483, 1886.

3. Baehr, G.; Shwartzman, G., and Greenspan, E. B.: Bacillus Friedländer Infections, Ann. Int. Med. **10**:1788, 1937.

Their series demonstrated a high incidence of biliary and renal infections which they explained by the tendency of the liver and kidney to excrete bacilli which had gained entry into the portal or systemic circulations. Infection appeared to be dependent on the existence of mechanical obstruction or stasis.

That Friedländer-aerogenes infections are ubiquitous can now be fairly well documented. Reports have appeared in which the organism was involved in primary suppuration of the liver,[4] primary peritonitis,[5] osteomyelitis,[6] acute salpingitis [7] prostatic abscess [8] and wound infections.[9] Several reports have implicated the organism as a cause of diarrhea in nursery infants [10] and in older children.[11] Faucett and Miller [12] described six infants with mouth lesions identical with thrush from all of which the Bacillus mucosus capsulatus was isolated although in three it was found in association with Monilia albicans. There was no systemic reaction to the infection, which remained resistant to local therapy but cleared promptly with sulfadiazine.

While it has been demonstrated that this group of organisms is capable of producing a wide variety of pathological lesions, their over-all occurrence as a cause of disease is apparently low. More exact bacteriologic determination, however, would probably reveal a greater incidence of infection caused by this group. Baehr, Shwartzman and Greenspan [8] have emphasized that when gram-negative rods are discovered in sputum, capsular staining is commonly performed with the resultant identification of the Friedländer bacillus as such. On the

4. Boettiger, C.; Weinstein, M., and Werne, J.: Primary Suppuration of the Liver Due to Friedländer's Bacillus, J. A. M. A. **114**:1050 (March 23) 1940.

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other hand, when gram-negative rods are isolated elsewhere, capsular staining is not likely to be done and the organisms are usually classified as members of the colon group. Further confusion may result from the similarity of the fermentation reactions between the Friedländer-aerogenes and the colon group. Solomon,[9] in a recent paper, has also decried the tendency to pass off all gram-negative bacilli as coliforms.

While more accurate bacteriologic verification might well reveal a relatively higher incidence of disease caused by the Friedländer-aerogenes group of organisms, evidence has been accumulating that the widespread use of penicillin may produce a real increase in these infections. Lipman, Coss and Boots [13] demonstrated that the daily oral administration of 1,000,000 units of penicillin over a period of months eliminated the normal gram-positive pharyngeal flora in ten patients with rheumatoid arthritis and permitted the appearance, in predominance, of gram-negative coliforms. The disappearance of penicillin-sensitive organisms followed by the overgrowth of gram-negative bacteria is responsible for the biological phenomenon of superinfection which occurs in the course of penicillin therapy. Several instances have now been recorded in which pathogenic pneumococci, in patients with pneumonia, have disappeared from the pharynx during penicillin therapy without a concomitant clinical cure.[14] Further bacteriologic study revealed the presence of Aerobacter aerogenes which responded to the use of streptomycin. A similar phenomenon, in reverse, has been described with streptomycin.[15]

Weinstein [14a] has pointed out that in most instances the alteration in flora occurs without the development of a new infection. In some patients, however, there occurs a rapid growth of the virulent, nonsusceptible strains which may have been present before in small numbers. He postulated that in these cases a high degree of bacterial antagonism exists by means of which some strains are held in check by others. The effect of the antibiotic is to disturb this relationship. Thus, penicillin, by eliminating the more susceptible gram-positive flora, in effect permits other pathogens, such as the Friedländer-aerogenes group, the opportunity of multiplication and invasion. Stanley [15a] has expressed the opinion that the relative absence of such secon-

13. Lipman, M. O.; Coss, J. A., Jr., and Boots, R. H.: Changes in the Bacterial Flora of the Throat and Intestinal Tract During Prolonged Oral Administration of Penicillin, Am. J. Med. **4**:702, 1948.

14. (*a*) Weinstein, L.: The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin, Am. J. M. Sc. **214**:56, 1947. (*b*) Appelbaum, E., and Leff, W. A.: Occurrence of Superinfections During Antibiotic Therapy, J. A. M. A. **138**:119 (Sept. 11) 1948.

15. (*a*) Stanley, M. M.: Bacillus Pyocyaneus Infections: A Review; Report of Cases and Discussion of Newer Therapy Including Streptomycin, Am. J. Med. **2**:253 and 347, 1947. (*b*) Weinstein.[14a]

dary infections during sulfonamide therapy is explained by the fact that these drugs are much less specific in their bacteriostatic properties and tend to prevent the growth of some gram-negative bacilli.

Wilhelm and Orkin [16] have reported a striking increase in the frequency of urinary tract infections caused by A. aerogenes. In the period from 1945 to 1948 they observed 126 positive urine cultures among 257 patients (49.2 per cent) with genitourinary infections, compared with 12 positive cultures among 163 similar patients (7.4 per cent) during 1940-1941. These authors postulated that the organism had become more virulent as evidenced by a greater degree of symptomatology among the patients in the later group. Subsequently, the same authors and their colleagues [17] reported finding A. aerogenes in 75 per cent of their patients with genitourinary infections. Significantly, bacteremia occurred in 24, and seven of this group died. Grotts [18] has recently described seven cases of Friedländer pneumonia in infants occurring over a four month period. Whether or not these reports indicate a real or apparent increase in infections of this type cannot be determined. They do, however, justify greater awareness as to the possibility of their occurrence.

The paucity of reports in the pediatric literature of Friedländer-aerogenes infections suggests that the incidence of these diseases is even lower in children than in adults. However low this incidence may be, the advent of the modern chemotherapeutic and antibiotic era, with the development of greater drug specificity, has made mandatory the more precise determination of etiological relationships. When the sulfonamides were the sole effective drugs available for the treatment of bacterial disease, there was, perhaps, justification for their use against any and all types of infection. But with the introduction of penicillin, streptomycin, aureomycin and chloramphenicol, each with a more or less definitive spectrum of antibiotic activity, bacteriologic identification has assumed practical therapeutic implications. Because some of the newer drugs have been demonstrated to be curative in cases of Friedländer-aerogenes infections, it is now necessary to look for these organisms, especially in those patients not responding to the administration of sulfadiazine and penicillin.

Our experience, which includes 10 cases of infections in infants over a 12 month period, is most interesting in view of the apparent infre-

16. Wilhelm, S. F., and Orkin, L. A.: The Increased Pathogenicity of Bacillus Lactis Aerogenes in Urinary Tract Infections, J. Urol. **61**:131, 1949.

17. Wilhelm, S. F.; Schloss, W. A.; Orkin, L. A.; Seligman, E., and Wassermann, M.: Aerobacter Aerogenes Infection of the Urinary Tract: Effective Treatment with Aureomycin; J. A. M. A. **141**:837 (Nov. 19) 1949.

18. Grotts, B. F.: Pneumonia in Infancy Caused by Friedländer's Bacillus, J. Pediat. **34**:174, 1949.

quency with which this group of organisms has, until recently, been encountered as a cause of disease in children. It also lends credence to the contention that one may anticipate an increase in these infections generally. The 10 patients include three with pneumonia, five with sepsis and one each with meningitis and a urinary tract infection. The 10 cases may be considered as primary in that they are not examples of institutional cross infection. The patients were hospitalized at different

TABLE 1.—*Summary of Data on Ten Patients with Friedländer-Aerogenes Infections*

Case	Clinical Type	Age	Source of Organism	Specific Drug Therapy	Outcome	Remarks
1	Pneumonia	15 mo.	Throat	Penicillin; streptomycin; aureomycin	Recovered	Coma and convulsions at onset; residual pleural thickening
2	Pneumonia	14 mo.	Throat; blood	Sulfadiazine	Recovered	.....
3	Pneumonia	6 mo.	Throat	Penicillin; streptomycin	Recovered	.....
4	Meningitis	5 wk.	Ventricular fluid	Streptomycin	Recovered from meningitis	Died of progressive hydrocephalus 9 mo. later
5	Genito-urinary infection	Newborn	Blood; urine	Sodium sulfadiazine	Died	Jaundice at birth; hydroureter and hydronephrosis; congenital heart disease; mongolism
6	Sepsis	2 mo.	Blood; urine	Sulfadiazine; streptomycin; chloramphenicol	Recovered	Premature; jaundice; well at time of onset
7	Sepsis	3 wk.	Throat; blood*; spinal fluid*	Penicillin	Died	Jaundice; preceding severe diarrhea
8	Sepsis	Newborn	Spinal fluid*	Penicillin	Died	Premature
9	Sepsis	Newborn	Blood*; spinal fluid*	.....	Died	Premature; extensive intracranial hemorrhage
10	Sepsis	Newborn	Blood; abscess	Sulfadiazine; penicillin; streptomycin; aureomycin; chloramphenicol	Died	Atresia of colon; colostomy, cecostomy; jaundice; peritonitis; meningitis at autopsy

* Culture taken immediately after death.

times or in widely separated wards with no possibility of contact. The significant data in all 10 cases are tabulated in table 1.

BACTERIOLOGY

1. *Cultural and Immunologic Characteristics.*—The Friedländer bacillus has been described under a variety of names, including Klebsiella pneumoniae, Bacillus mucosus capsulatus and pneumobacillus. A. aerogenes has also been designated as Bacterium aerogenes and Bacillus lactis aerogenes. Both organisms are gram-negative, nonmotile, encapsulated rods, which are somewhat pleomorphic, occasionally grow in short chains and characteristically produce stringy, mucoid colonies. These morphologic and cultural features as well as the bio-

chemical and serologic similarities to be discussed below have led to the conclusion that the Friedländer bacillus and A. aerogenes are closely related if not identical. The former name is usually attached to the organism isolated from the respiratory tract; the latter, to that found in the intestine or urinary tract. This distinction, based solely on the site from which they are isolated, does not seem to be a valid method of separation of the organisms in view of the many other similarities.

Perkins,[19] along with others, has concluded that the fermentation of various sugars for diagnostic classification is of no value, and Fitzgerald[20] was unable to establish any clear differences between these organisms by the use of differential mediums, by fermentation reactions, or by agglutination or complement fixation methods. Biochemical tests have also been unsuitable as a basis for differentiation since strains thought to be serologically identical have shown marked differences in their reactions.[21] Edwards[22] has also demonstrated that A. aerogenes and K. pneumoniae may show similar chemical and fermentation reactions and suggested that, since no constant differences have been found which permit distinctions to be made between them, they be included in a single genus.

In 1918, Blake[23] found, in a patient with Friedländer pneumonia, that a soluble antigen was present in the blood and in the urine from the fifth to the eighth day of the disease. Avery, Heidelberger and Goebel[24] subsequently showed this to be a polysaccharide not unlike that found in the capsule of the pneumococcus. Julianelle[25] later demonstrated by means of agglutination, adsorptive agglutination and precipitin tests that three serologic types of Friedländer bacilli, designated

19. Perkins, R. G.: Bacillus Mucosus Capsulatus: A Study of the Group and an Attempt at Classification of the Varieties Described, J. Infect. Dis. **1**:241, 1904; Relation of Bacillus Mucosus Capsulatus Group to Rhinoscleroma and of the Various Members of the Group to One Another, ibid. **4**:51, 1907.

20. Fitzgerald, J. G.: A Biometrical Study of the Mucosus Capsulatus Group, J. Infect. Dis. **15**:268, 1914.

21. (*a*) Julianelle, L. A.: The Distribution of Friedländer's Bacilli of Different Types, J. Exper. Med. **52**:539, 1930. (*b*) Edwards, P. R.: The Relation of Encapsulated Bacilli Found in Metritis in Mares to Encapsulated Bacilli from Human Sources, J. Bact. **15**:245, 1928.

22. Edwards, P. R.: Relationships of the Encapsulated Bacilli with Special Reference to Bact. Aerogenes, J. Bact. **17**:339, 1929.

23. Blake, F. G.: Antigen-Antibody Balance in Lobar Pneumonia, Arch. Int. Med. **21**:779 (June) 1918.

24. Avery, O. T.; Heidelberger, M., and Goebel, W. F.: Soluble Specific Substance of Friedländer's Bacillus: Chemical and Immunological Relationships of Pneumococcus Type II and of Strain of Friedländer's Bacillus, J. Exper. Med. **42**:709, 1925.

25. Julianelle, L. A.: A Biological Classification of Encapsulatus Pneumoniae (Friedländer's Bacillus), J. Exper. Med. **44**:113, 1926.

A, B and C, could be distinguished. However, many strains could not thus be separated, necessitating a heterogeneous group X. In a subsequent study, Julianelle[21a] showed that there is no correlation between the serologic type and fermentation activity and that the fermentation reactions were not reliable in distinguishing the Friedländer bacillus from closely allied organisms.

Edwards,[22] working with encapsulated gram-negative rods obtained from human patients and from mares, found that A. aerogenes, certain equine organisms, granuloma bacilli and Friedländer bacilli all agglutinated with a Friedländer antiserum. The same results were obtained with precipitin tests involving group nucleoprotein reactions. Rake,[26] by means of complement fixation tests performed with antigens prepared from strains designated as K. pneumoniae, A. aerogenes, granuloma bacilli and Escherichia coli, demonstrated that these organisms were allied to one another.

It is interesting at this point to quote Hay in regard to the historical reasons for the separation of A. aerogenes and the Friedländer bacillus into separate groups. "Much of the difficulty arose from the fact that Friedländer's bacillus, one of the first members of the group to be isolated (1882), was studied from a morphological standpoint, while Escherich, who described B. lactis aerogenes in 1886, stressed its biological similarity to B. coli. A chasm was thus created between B. lactis aerogenes and Friedländer's bacillus which has not been bridged to the present day, although these organisms must always have resembled more than they differed from each other." [27]

Traditionally, A. aerogenes has been considered to be closely related to the coliform organisms, and the group is often referred to as coli-aerogenes. If the Friedländer bacillus is indistinguishable from A. aerogenes, it must also be similarly allied to the colon group. The recent studies of Osterman and Rettger,[28] in addition to confirming the earlier conclusion of Edwards in regard to the unreliability of morphologic and cultural characteristics in differentiating these organisms, emphasized the close immunologic and biochemical relationships between the Friedländer bacillus and A. aerogenes and between these two and certain forms of E. coli.

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26. Rake, G.: A Further Note on the Antigenic Relationships of Donovania Granulomatis (Anderson), J. Bact. **55**:865, 1948.

27. Hay, H. R.: A Study of the Bacillus Mucosus Capsulatus Group, J. Hyg. **32**:240, 1932.

28. (*a*) Osterman, E., and Rettger, L. F.: A Comparative Study of Organisms of the Friedländer and Coli-Aerogenes Groups: I. Morphological and Cultural Characteristics, with Emphasis on Variation, J. Bact. **42**:699, 1941. (*b*) Osterman, E., and Rettger, L. F.: Comparative Study of Organisms of Friedländer and Coli-Aerogenes Groups: II. Pathogenicity, Biochemical Reactions, and Serological Relationships, ibid. **42**:721, 1941.

All three organisms may occur as mucoid, smooth and rough colonies designated as M, S, and R phases. The Friedländer bacillus and A. aerogenes are ordinarily isolated in nature in the M, or encapsulated, phase, whereas E. coli normally exists in the S, or nonencapsulated, phase.[28a] Osterman and Rettger were unable to discover any differences in organisms or colonies when all three were in the M, S or R phase. Randall [29] had noted earlier that under certain conditions members of the colon group may assume the mucoid form and that the Friedländer bacillus when decapsulated produces the smooth translucent colony characteristic of the colon bacillus. In the latest classification of Bergey [30] the Tribe Escherichae includes *Genus I.* Escherichia, *Genus II.* Aerobacter, and *Genus III.* Klebsiella.

Under conditions which obtain normally, the absence of a capsule would appear to separate E. coli from A. aerogenes and the Friedländer bacillus. It has been established that the latter two organisms are closely related morphologically, culturally, biochemically and antigenically. They have a common group nucleoprotein and an individual capsular polysaccharide which gives some strains a type specificity similar to that of the pneumococcus. It is for these reasons that we are considering the gram-negative rods isolated in our patients as organisms of the Friedländer-aerogenes group rather than as one or the other.

2. Distribution of the Friedländer-Aerogenes Organisms.—The Friedländer-aerogenes organisms are widely distributed in nature. In man there are two main sites of localization, the intestinal and respiratory tracts, in both of which they may exist in the carrier state. Of the two, the intestinal localization is the more frequent.

The organism has been found in the soil, even where fecal contamination by man and animals was considered unlikely, in the water supply of a large municipality, in milk and in flies.[31] It has been isolated from the gastrointestinal tracts of healthy persons with variable frequency.[32] It is difficult to explain the wide divergence in the incidence of the carrier state between 5.5 per cent quoted by Dudgeon [32a] and 97 per cent found by Gray [31a] except as a consequence of the small size of the

29. Randall, W. A.: Colony and Antigenic Variation in Klebsiella Pneumoniae Types A, B and C, J. Bact. **38**:461, 1939.

30. Bergey, D. H.: Bergey's Manual of Determinative Bacteriology, edited by R. S. Breed, E. G. Murray and A. P. Hitcheno, ed. 6, Baltimore, Williams & Wilkins Company, 1948.

31. (*a*) Gray, J. D. A.: The Significance of Bact. Aerogenes in Water, J. Hyg. **32**:132, 1932. (*b*) Hay.[27]

32. (*a*) Dudgeon, L. S.: A Study of the Intestinal Flora Under Normal and Abnormal Conditions, J. Hyg. **25**:119, 1926. (*b*) Unpublished communication by Cruikshank cited by Gray.[31a] (*c*) Mollari, M.; Randall, W. A., and Reedy, R.: The Incidence of Bacterium Aerogenes and Intermediates in Human Feces, J. Trop. Med. **42**:34, 1939. (*d*) Hay.[27] (*e*) Gray.[31a]

samples. Since Hay [27] was able to recover the organism only from the surface mucus of the stool specimens, she concluded that its natural habitat was the large bowel. Baehr, Shwartzman and Greenspan [8] in their series demonstrated positive peritoneal cultures in 61 patients with perforative lesions of the intestine.

Few studies have been done to establish the incidence of healthy respiratory carriers. Except for Bloomfield,[33] who found the organism in five of 85 unselected hospital patients (5.5 per cent), the frequency with which the organism can be recovered in patients without respiratory disease is considerably less than 1 per cent.[34] In patients with respiratory disease the incidence of positive cultures was only 2.5 per cent.[35] Faucett and Miller [12] and Grotts [15] were able to demonstrate the organism only in those patients with pulmonary infection.

PULMONARY INFECTIONS

During the past three decades several comprehensive reports of Friedländer's pneumonia in adults have appeared, and the reader is referred to them for their very complete bacteriologic, clinical, pathologic and roentgenographic descriptions of the disease.[36] The adult type of pulmonary infection occurs in an acute and in a chronic form.

The acute form resembles pneumococcic pneumonia and usually begins suddenly with a chill, pleuritic pain, hemoptysis and a productive cough. The sputum is usually abundant, blood tinged, mucoid in character and very tenacious. Large numbers of encapsulated gram-negative bacilli can usually be seen on direct smear, and, while other organisms

33. Bloomfield, A. L.: The Mechanism of the Bacillus Carrier State with Special Reference to the Friedländer Bacillus, Am. Rev. Tuberc. **4**:847, 1921.

34. (*a*) Hyde, L., and Hyde, B.: Primary Friedländer Pneumonia, Am. J. M. Sc. **205**:660, 1943. (*b*) Faucett and Miller.[12] (*c*) Grotts.[15]

35. Bullowa, J. G. M.; Chess, J., and Friedman, N. B.: Pneumonia Due to Bacillus Friedländeri: A Report on 41 Patients, with Consideration of Specific Serum Therapy, Arch. Int. Med. **60**:735 (Nov.) 1937.

36. (*a*) Belk, W. P.: Pulmonary Infections by Friedländer's Bacillus, J. Infect. Dis. **38**:115, 1926. (*b*) Kornblum, K.: The Roentgen-Ray Diagnosis of Pulmonary Infection with the Friedländer Bacillus, Am. J. Roentgenol. **19**:513, 1928. (*c*) Collins, L. H., Jr., and Kornblum, K.: Chronic Pulmonary Infection Due to the Friedländer Bacillus: A Clinical and Roentgenologic Study, Arch. Int. Med. **43**:351 (March) 1929. (*d*) Solomon, S.: Primary Friedländer Pneumonia; Report of 32 Cases, J. A. M. A. **108**:937 (March 20) 1937. (*e*) Chronic Friedländer Infections of the Lung; Report of 17 Cases and Observations on Therapy with Sulfapyridine and Sulfanilamide, ibid. **115**:1527 (Nov. 2) 1940. (*f*) Julianelle, L. A.: The Pneumonia of Friedländer's Bacillus, Ann. Int. Med. **15**:190, 1941. (*g*) Perlman, E., and Bullowa, J. G. M.: Primary Bacillus Friedländer (Klebsiella Pneumoniae) Pneumonia: Therapy of B. Friedländer B Pneumonia, Arch. Int. Med. **67**:907 (May) 1941. (*h*) Hyde and Hyde.[34] (*i*) Bullowa, Chess and Friedman.[35]

may be present, the Friedländer bacillus is predominant and may often be grown in pure culture. Pathologically, the disease begins as an undifferentiated bronchopneumonia which soon becomes confluent, showing a pseudolobar distribution with small areas of normal lung tissue intervening throughout. Pleural involvement may be extensive. The characteristic pathologic feature is the early and widespread necrosis leading to the formation of gross and microscopic abscesses and cavities. Belk [36a] noted the abscesses as early as the fourth day of illness and was the first to describe their characteristic thin-walled appearance on the roentgenogram. In the event of recovery, fibrosis takes place. These pathologic changes have been correlated with the roentgenographic findings by Kornblum.[36b] Bacteremia, which occurs in a large number of the cases, is quite transient.[36d] Both Solomon [36d] and Perlman and Bullowa [36g] found no correlation between bacteremia and mortality.

Until the advent of streptomycin the disease ran a rapidly fulminating course, with death occurring during the stage of widespread tissue necrosis. The composite mortality from several published series by different authors, as cited by Julianelle,[36f] was 82 per cent. We are not aware of any extensive series of cases in adults treated with streptomycin, but individual instances of recovery following the administration of this antibiotic have been reported.[37]

The chronic form of the disease may have an insidious onset or may begin as a typical case of acute Friedländer pneumonia. In Solomon's series of 17 patients, the disease began acutely in all save three.[36e] Of those who survive the acute phase, a few may recover completely. The remainder pass into the chronic stage, which is protracted but relatively benign. There is chronic pulmonary suppuration with abscess formation, cavitation, bronchiectasis and fibrosis. The resemblance to pulmonary tuberculosis has been remarked on by several authors.[38] Complete resolution may occur or there may be remissions and exacerbations. Brock,[39] quoting Brulé and his associates, cited a case extending over a period of nine years. The mortality in the chronic form in Solomon's [36e] series was 23.5 per cent, as compared with a mortality of 97 per cent in his patients with the acute disease.[36d] The incidence of bacteremia was 31 per cent in the chronic group, as compared with 70 per cent in the acute group.

37. Learner, N., and Minnich, W. R.: Friedländer Pneumonia Treated with Streptomycin: Report of a Case with Prompt Recovery, Ann. Int. Med. **25**:516, 1946. Bishop, C. A., and Rasmussen, R. F.: Klebsiella Pneumonia Treated with Streptomycin, J. A. M. A. **131**:821 (July 6) 1946. Davis, J. P.; Cheek, K. M., and Harrell, G. T., Jr.: Friedländer's Pneumonia with Bacteremia Successfully Treated with Streptomycin, North Carolina M. J. **8**:767, 1947.

38. Bullowa, Chess and Friedman.[35] Belk.[36a] Kornblum.[36b]

39. Brock, R. C.: Studies in Lung Abscess, Guy's Hosp. Rep. **95**:40, 1946.

Two cases of Friedländer's pneumonia in children were reported more than 50 years ago by Étienne [40] and Comba.[41] Both cases ended fatally. Dunn and Hammond [42] described the case of a 14 month old infant with a pleural effusion in whom inadvertent lung puncture during a thoracentesis was the source of a positive culture. The organism was subsequently demonstrated again, and this patient recovered. Kliewe [43] described an institutional epidemic in which pneumonia developed in 11 of 12 infants in a single ward and the Friedländer bacillus was cultured from the pharynx of all 11. Two children died, and in one the organism was isolated from the lungs at necropsy. Of the remaining 130 children in the institution, only one had a positive throat culture.

Occurrence of the disease in infant twins was reported by Ferguson and Tower.[44] One infant, whose chest roentgenogram showed suggestive cavity formation in addition to patches of bronchopneumonia, died and the organism was present in the lungs at necropsy. The twin, whose throat yielded a pure culture of the Friedländer bacillus, recovered. Vomiting and diarrhea were prominent symptoms in both, but results of stool cultures were not reported.

Thus, of the 16 children with Friedländer pneumonia reported on before the advent of the sulfonamides, 11 recovered. It cannot, however, be said from this small number of patients that the disease in infants necessarily carries a lower mortality than in adults. This group is heavily weighted by the 11 patients of Kliewe, and it may well be that the virulence of that particular strain of the organism was low. Nevertheless, the survival rate of *69* per cent without specific therapy should be kept in mind when the effects of the newer antibiotics are being evaluated.

In 1947 Miller, Orris and Taus [45] reported the case of a 3 week old infant with pneumonia who failed to respond to penicillin and sulfadiazine. When the throat culture revealed the Friedländer bacillus, streptomycin was administered and recovery ensued. Rales could still be heard, however, several weeks later, and cystic changes in the lung

40. Étienne, G.: Le pneumo-bacille de Friedländer: Son rôle en pathologie, Arch. de méd. expér. et d'anat. path. **7**:124, 1895.

41. Comba, C.: Un caso di setticemia da bacillo del Friedländer in un neonato associata a sclerema (contributo alla patogenesi dello sclerema), Arch. de biol. **1**:112, 1896.

42. Dunn, C., and Hammond, J.: A Case of Friedländer's Pneumonia with Recovery, Interstate M. J. **22**:1133, 1915.

43. Kliewe, H.: Epidemiologische und biologische Studien über den B. pneumoniae Friedländer und verwandte Arten, Zentralbl. f. Bakteriol. (Ab. 1) **116**:92, 1930.

44. Ferguson, J. A., and Tower, A. A.: Pneumonia in Infants, Due to Bacillus Mucosus-Capsulatus, Am. J. Dis. Child. **46**:59 (July) 1933.

45. Miller, B. W.; Orris, H. W., and Taus, H. H.: Friedländer's Pneumonia in Infancy, J. Pediat. **31**:521, 1947.

were present on the roentgenogram. This is the only instance so far reported in which the clinical course of the disease in a child resembled chronic Friedländer's pneumonia as seen in adults.

Grotts [16] has recently recorded his experience with seven cases of Friedländer pneumonia in infants, the oldest of whom was aged 13 months. One recovered with sulfadiazine, while the remaining six recovered with streptomycin after failure to do so with sulfadiazine or penicillin or both. In none of these patients did abscesses or cavities develop, although in two auscultatory signs of continued infection persisted for weeks and culture of the throat continued to show the Friedländer bacillus at the time of writing. All seven had some vomiting or diarrhea or both. While the tendency of infants toward development of gastrointestinal disturbances with systemic infections is well known, it is interesting to note that nine adults in Solomon's [86d] series also had these symptoms which may possibly be related to intestinal invasion by the organism. Unfortunately, no stool cultures were reported.

REPORT OF CASES OF PNEUMONIA

In three of our patients pneumonia developed.

CASE 1.—K. G., a 15 month old boy, was admitted to Charity Hospital on Jan. 11, 1949, with a history of a respiratory infection of two weeks' duration. Birth and the neonatal period were uncomplicated; growth and development had been normal; the family history was noncontributory. This, the patient's first illness, began on Dec. 28, 1948, two weeks before admission, with a nasal discharge, followed on the next day by development of cough and fever. The symptoms progressed until January 2, when he was admitted to a hospital in another city and a diagnosis of pneumonia was made. Therapy consisted of a daily intramuscular injection of 300,000 units of procaine penicillin in oil and was continued until January 6, when it became necessary for the family to return to New Orleans. On the same day he was seen in the admitting room of Charity Hospital, where a roentgenogram revealed an area of infiltration in the lower lobe of the left lung adjacent to the cardiac border. He was allowed to return home, but daily intramuscular injections of 300,000 units of procaine penicillin in oil were continued for five days. He showed very little response to therapy, the temperature fluctuating between 100 and 104 F. daily. The cough persisted, appetite was poor and vomiting occurred occasionally. He was therefore admitted.

Physical Examination.—On admission the temperature was 100 F. and weight was 19 pounds 4 ounces (8,730 Gm.). The patient was a well developed, well nourished infant appearing acutely ill but in no respiratory distress. Both tympanic membranes were diffusely reddened, but the landmarks were still visible. The pharynx and tonsils were congested but without exudate. The anterior and posterior cervical lymph nodes were enlarged. There were dulness and diminished breath sounds over the left lower part of the chest posteriorly and numerous fine rales scattered over both lung fields. The spleen was palpable 2 cm. and the liver 3 cm. below the costal margin. Neurologic examination demonstrated normal deep and superficial reflexes with no pathologic responses.

Laboratory Data.—The hemoglobin content was 12 Gm., red blood cell count 4,980,000 and white blood cell count 6,000 with 49 per cent polymorphonuclear

leukocytes and 51 per cent lymphocytes. Urinalysis revealed a 3+ reaction for albumin and an occasional hyaline cast. Results of a serologic test for syphilis, a tuberculin test with old tuberculin (1:1,000), and one sputum examination for acid-fast bacilli were all negative. Two blood cultures demonstrated no growth. Stool and urine cultures were negative for Shigella and Salmonella. Blood agglutination studies for typhoid, paratyphoid and brucellosis were negative. The cold agglutinin titer was 1:40. A roentgenogram of the chest revealed an extension of the previously described infiltration in the lower lobe of the left lung.

Course.—A diagnosis of pneumonia and bilateral otitis media was made. Because of the patient's previous failure to respond to penicillin he was given 1.8 Gm. of sulfadiazine daily. Twelve hours after admission he had a generalized convulsion. On the second hospital day the temperature ranged between 99 and 103 F. and two more convulsions occurred. Respirations were of the Cheyne-Stokes variety. Coma ensued and lasted some 30 hours, during which time there were occasional twitchings of the face and extremities. No meningeal signs were elicited, but there was some spasticity of all four extremities. Cyanosis developed but cleared under oxygen therapy. Lumbar puncture yielded clear fluid under a pressure of 260 mm. of water, with 3 lymphocytes per cubic milliliter and 27 mg. of protein and 182 mg. of glucose per 100 ml. The latter value was probably elevated as a result of the parenteral administration of dextrose. Blood urea nitrogen was 13.2 mg., serum calcium 8 mg. and phosphorus 5 mg. per 100 ml. The carbon dioxide content was 28.2 millimoles per liter. Because of the patient's desperate clinical condition, therapy with streptomycin and aureomycin was instituted despite the absence of any evidence that we were dealing with a susceptible organism. Streptomycin was administered intramuscularly, 60 mg. every four hours, and aureomycin was given orally, 250 mg. every six hours. Use of sulfadiazine was discontinued.

By the afternoon of the second day the patient was out of coma, alert but irritable. During the next two days the temperature continued to range between 99 and 103 F. On January 16, five days after admission, the nose and throat culture taken on entrance and one taken subsequently were reported as showing a predominant growth of an organism of the Friedländer-aerogenes group sensitive to both streptomycin and aureomycin. Pseudomonas aeruginosa, not sensitive to either antibiotic, was also present. By January 17 the patient had been afebrile for two days and his general condition had improved significantly, although signs of pneumonia were still apparent and roentgenographic evidence of infiltration was unchanged from that on admission. Because of a limited supply, the administration of aureomycin was discontinued. On January 21, because of clinical signs of a pleural effusion, the use of the drug was started again in the same dosage. However, on January 23 a roentgenogram of the chest failed to confirm the presence of fluid, and at this time use of both streptomycin and aureomycin was discontinued. On the following day varicella developed. On January 27 a review of the chest roentgenograms suggested the presence of a cavity within the area of consolidation in the lower lobe of the left lung, and both streptomycin and aureomycin were reintroduced in their original dosage. Their use was discontinued seven days later, and by February 4 all physical signs of pneumonia had cleared, although the roentgenogram still showed an extensive area of consolidation. After an afebrile period of two weeks the patient was discharged to be followed in the clinic. The subsequent roentgenograms of the chest did not sustain the initial impression of cavitation.

He was seen at intervals of two weeks. Weight gain was slow, but examination of the chest revealed normal auscultatory findings. Residual pleural thickening, however, has persisted up to the time of this report, even though the roentgenograms continued to show resolution of the consolidation. In July 1949 bronchographic study failed to demonstrate any bronchial dilatation.

Summary.—This 15 month old patient was treated for pneumonia with penicillin for two weeks with no significant response. Shortly after admission severe neurological manifestations developed. Streptomycin and aureomycin were administered. An organism of the Friedländer-aerogenes group was present in predominance on two successive pharyngeal cultures. He made a slow but progressive recovery with only residual pleural thickening remaining. He may be considered to have been severely ill.

CASE 2.—D. V., a 14 month old boy, was admitted to Charity Hospital on May 26, 1949, with a four day history of cough, fever, listlessness and anorexia and a one day history of diarrhea. He had been one of triplets and weighed 5 pounds (2,270 Gm.) at birth. The birth history and the neonatal period were uneventful save for the presence of a harelip and cleft palate, the former having been repaired without difficulty at the age of 4 months. In January 1949, the patient had been hospitalized because of a type XIV Pneumococcus pneumonia and meningitis. He responded well to sulfadiazine and penicillin therapy. A nose and throat culture during this illness, in addition to the type XIV Pneumococcus and the usual flora, showed an organism of the Friedländer-aerogenes group. The patient had been well during the interval of four months until admission.

Physical Examination.—The temperature was 102.4 F., the pulse rate was 140 and the respiration rate was 28 per minute. The patient was a well developed, poorly nourished infant boy with grunting, labored respiration. He appeared acutely ill and in distress. The anterior fontanel was open and of normal tension. Both tympanic membranes were dull, and the landmarks were obscure. There was obvious flaring of the alae nasi, and a bilateral mucoid nasal discharge was present. There was a scar over the site of the repaired hare lip on the left. The posterior portion of the hard palate and the entire soft palate were cleft in the midline. The pharynx and tonsils were reddened. There was slight subcostal retraction with impaired resonance and diminished breath sounds over the upper left part of the chest anteriorly and the lower right part of the chest posteriorly. There were fine rales over the right side. A loud, harsh systolic murmur was present over the apex with no significant radiation. Sounds were of good quality, the rhythm was regular, and there was no thrill. The murmur was thought to represent an interventricular septal defect. Abdominal and neurological examinations were unrevealing.

Laboratory Data.—The hemoglobin concentration was 11.5 Gm.; red blood cell count, 4,070,000; white blood cell count, 18,100, with 68 per cent neutrophilic leukocytes, 1 per cent eosinophils, 1 per cent mononuclears and 30 per cent lymphocytes. Urinalysis gave normal values. Results of a serologic test for syphilis and a tuberculin test with old tuberculin (1:1,000) were negative.

Course.—A diagnosis of bilateral bronchopneumonia was made, and treatment was started with 1.8 Gm. of sulfadiazine daily. The temperature fell precipitously to 99 F. on the evening of admission and remained normal throughout the remainder of the patient's course in the hospital. The pulmonary findings cleared rapidly. On May 31, five days after admission, the use of sulfadiazine was discontinued. Two days later the blood culture taken on admission was reported positive for an organism of the Friedländer-aerogenes group sensitive to 1 microgram of streptomycin. Unfortunately, its sensitivity to sulfadiazine was never established. A nose and throat culture also taken on admission revealed the same organism in addition to an alpha hemolytic Streptococcus and Staphylococcus pyogenes aureus. Because of the rapid response to therapy no further cultures were taken.

Summary.—The patient, a 14 month old boy, was hospitalized after an illness of four days with bilateral bronchopneumonia. He was acutely ill on admission and in respiratory distress. The clinical response to sulfadiazine was prompt and dramatic. After his recovery and the discontinuance of sulfadiazine therapy, blood and pharyngeal cultures were reported as showing an organism of the Friedländer-aerogenes group. In contrast to the severe illness of the patient described in case 1, this patient may be said to have had a mild illness.

CASE 3.—J. M., a 6 month old girl, was admitted to the hospital on Feb. 28, 1949, because of fever, cough and vomiting of three days' duration. These symptoms persisted until admission. Delivery had occurred at term, and there were no natal or neonatal complications. The birth weight was 7 pounds 10 ounces (3,470 Gm.). Growth and development had been normal and the diet adequate.

Physical Examination.—The temperature was 105.4 F., pulse rate 200, respiration rate 60 and weight 17 pounds 1 ounce (7,740 Gm.). The patient was well developed and well nourished, alert and acutely ill. The anterior fontanel was open, 1 cm. wide, and of normal tension. Both tympanic membranes were reddened, and the landmarks were obscure. There was a seromucoid nasal discharge, and the pharynx was congested. The neck was supple, with no significant lymphadenopathy. Except for tachycardia, the heart was normal. The chest was clear except for some impaired resonance, bronchovesicular breath sounds and fine crepitant rales below the left scapula. Findings on abdominal and neurological examination were normal.

Laboratory Data.—The hemoglobin concentration was 11.5 Gm.; red blood cell count, 4,130,000, and white blood cell count, 8,600, with 74 per cent granulocytes, of which half were nonsegmented, and 26 per cent lymphocytes. The urine was normal. A serologic test for syphilis as well as the tuberculin test with old tuberculin (1:100) gave a negative reaction. The cold agglutinin titer was 1:8, and the blood culture on admission was sterile. A roentgenogram of the chest revealed the presence of bilateral infiltration with the greatest involvement in the lower part of the left lung field in the pericardiac region.

Course.—A diagnosis of bronchopneumonia and otitis media was made on admission, and an attempt was made to treat the patient with a single large dose of penicillin. Accordingly, 100,000 units of penicillin in aqueous solution was administered intramuscularly soon after her arrival in the ward. The temperature dropped precipitously to 99.4 F. on the second day but promptly rose again to 103 F. Since the patient remained febrile and acutely ill for three days, a course of penicillin consisting of 20,000 units given every 12 hours was started on March 2. Despite antibiotic therapy, the temperature continued to fluctuate between 100 and 103 F. On March 5, six days after admission, the nose and throat culture, taken on entrance to the hospital, was reported as showing a predominant growth of an organism of the Friedländer-aerogenes group with a few colonies of beta hemolytic Streptococcus. At this point, penicillin therapy was stopped, and injection of streptomycin, 80 mg. intramuscularly every six hours, was begun. After the institution of streptomycin therapy the patient's temperature fell from 101 to 98.6 F. in 24 hours and remained normal until March 14, nine days later, when use of the drug was discontinued. A nose and throat culture on the same day revealed the presence of staphylococci, a bile-soluble untypable Pneumococcus and a few colonies of the Friedländer-aerogenes organism. Clinically the patient appeared well, although an infiltration was still demonstrable on the roentgenogram.

On March 18 there developed an episode of asthmatic bronchitis associated with fever which responded to 0.25 Gm. of sulfadiazine every four hours and to antispasmodics. Six days later, on March 24, acute otitis media developed; it was successfully treated with penicillin. The nose and throat culture at this time, while badly overgrown, gave no evidence of the presence of the Friedländer-aerogenes organism. The use of penicillin was discontinued on March 28 and on April 4, when the patient was discharged, a roentgenogram showed complete resolution of the pulmonary infiltration. She was seen in the clinic the following week and appeared well.

Summary.—This patient, a 6 month old girl, was ill for three days and on entrance to the hospital had clinical and roentgenographic evidence of bilateral bronchopneumonia. She did not respond to a single large dose of penicillin or to penicillin administered every 12 hours for three days. After a Friedländer-aerogenes bacillus had been identified in the nose and throat culture, streptomycin therapy was begun and the patient made a prompt recovery. Subsequently she had asthmatic bronchitis and otitis media, which responded to sulfadiazine and penicillin respectively. She presents a moderately severe Friedländer pneumonia.

Less than 30 cases of acute Friedländer pneumonia in children have been reported to date. The incidence appears to be lower than in adults, although most certainly many cases have not been reported. Whether more persistent search would reveal a higher incidence still remains to be seen. In children the disease is peculiarly one of infancy, the oldest patient reported having been 15 months of age. Pathologically there is not the same tendency toward necrosis and abscess formation as is seen in adults. Only one case resembling the chronic Friedländer pneumonia in adults has been encountered in childhood, although longer follow-up study of some of the more recently described cases may yield evidences of chronicity.

Even in the era before specific chemotherapy the mortality in children appeared to be lower than that in adults. Eleven of the 16 patients reported before the introduction of the sulfonamides recovered. The 11 patients reported subsequently, including the three recorded here, all survived. In nine of the latter group sulfadiazine or penicillin or both proved completely ineffectual, recovery resulting only after the use of streptomycin. In two instances of recovery the only specific therapeutic agent employed was sulfadiazine.

Clinically, the disease is indistinguishable from other bacterial pneumonias and is established only by the isolation of the causative organism. This often comes as a surprise in case of a patient who is not making the expected progress on sulfadiazine or penicillin. The mucoid, tenacious sputum seen so characteristically in adults is not so readily obtained from children. There is nothing typical of the course of the disease or the laboratory findings. The characteristic pulmonary roentgenographic changes described by Belk [36a] and Kornblum [36b] for adults

have not as a rule been seen in children. All grades of severity are encountered. In two of the patients described by Grotts [10] and the patient reported on here as case 1 severe neurological manifestations with convulsions developed in the presence of normal spinal fluid cytology and chemistry.

It is always difficult to establish the causal relationship between the organism isolated from the nasopharynx and the pathological process in an adjacent or distant communicating focus. The pathogenesis of the respiratory infection requires that the organisms be transported from an external source to the patient, that they begin to multiply and are not disposed of immediately on reaching the respiratory mucosa and, lastly, that they invade the body and set up an inflammatory process.[46] The organism found in the nasopharynx in a patient with disease of the lower respiratory tract may be the causative agent. On the other hand, it may not be at all related. Its presence in the nasopharynx is only presumptive, not definitive, evidence of etiological relationship.

Bloomfield,[46] by means of serial cultures which were designed to delineate the nature of the normal pharyngeal flora, established that there are three distinct groups of organisms commonly encountered in the upper respiratory tract. There are the organisms which are normally present and constitute the basic flora: nonhemolytic streptococci, gram-negative cocci and diphtheroids. In addition, there is a transient flora of nonpathogenic or potentially pathogenic bacteria present only for short periods. Lastly, there are foreign organisms "carried" for long periods, usually in a local nidus of infection.

In a series of experiments Bloomfield [47] further attempted to alter the normal flora by implanting Escherichia coli, Staphylococcus albus, Hemophilus influenzae and the Friedländer bacillus on the upper respiratory tracts of persons free of any infection. These organisms could not be detected after 24 to 48 hours, and he attributed their disappearance to the destructive effect of the mouth secretions and the mechanical flushing processes in the nose and mouth. These artificially implanted bacteria have their counterpart in normal circumstances in the transient flora mentioned above. The occasional presence of the Friedländer bacillus in the pharynx may represent this type of transient flora.

In his implantation experiments using the Friedländer bacillus, Bloomfield [47c] was unable to produce the carrier state or to induce local

46. Bloomfield, A. L.: The Localization of Bacteria in the Upper Air Passages: Its Bearing on Infection, Bull. Johns Hopkins Hosp. **32**:290, 1921.

47. (*a*) Bloomfield, A. L.: The Fate of Bacteria Introduced into the Upper Air Passages: II. B. Coli and Staphylococcus Albus, Bull. Johns Hopkins Hosp. **31**:14, 1920; (*b*) The Fate of Influenza Bacilli Introduced into the Upper Air Passages, ibid. **31**:85, 1920; (*c*) The Fate of Bacteria Introduced into the Upper Air Passages: V. The Friedländer Bacilli, ibid. **31**:203, 1920.

or systemic disease in healthy subjects. The organisms were not recoverable after 24 hours. On the other hand, he was able to culture the Friedländer bacillus from the throats of two subjects over a period of months, in the absence of preceding or current infection. From his work, Bloomfield concluded that the bacillus is rarely found in the upper air passages of healthy people, that when present it may persist for some time, that it rarely produces disease but will occasionally set up a fulminating pathological process and that it is largely a secondary invader. Subsequently, however, he summarized the situation by stating that when any organism, apart from the normal flora, is found repeatedly in the pharynx it may be indicative of disease.[48]

It would seem, therefore, that it is difficult to establish a diagnosis of Friedländer pneumonia solely on the basis of bacteriologic identification of the organism on pharyngeal culture. Perlman and Bullowa [36g] included the following criteria as helpful in establishing the diagnosis: clinical and roentgenographic evidence of pulmonary consolidation, repeated demonstration of the organism in the sputum in the absence of other etiologic agents, positive blood cultures, positive antemortem or postmortem aspirates from the lung and demonstration of specific capsular polysaccharide in the blood and urine. We did not perform diagnostic lung punctures or polysaccharide determinations. In one of our patients (case 2) all the first three criteria were fulfilled. In the remaining two patients, the Friedländer bacillus was found only in the throat. However, the failure to recover with penicillin, the prompt response to streptomycin and the disappearance of the organisms from the throat after administration of this antibiotic seem to us indicative of a causal relation between the presence of the bacillus and the pneumonia. The fact that the organism was isolated in pure culture or predominance may also be significant.

In the patient described in case 1 the Friedländer pneumonia may have been present from the onset, in which case there is the possibility that a bacteremia may have occurred during the two week period prior to hospitalization. On the other hand, one may argue with equal justification that the Friedländer bacillus represents a superinfection as a consequence of penicillin therapy in a patient whose pneumonia may well have been coccic in origin.

Some authors [49] are of the opinion that the Friedländer bacillus, in its role as a respiratory pathogen, is a secondary invader of a previously diseased focus. One need not be concerned with establishing the priority of the Friedländer-aerogenes organism in any given lesion so far as therapy is concerned. Whether it is a primary or a secondary invader

48. Bloomfield, A. L.: The Significance of the Bacteria Found in the Throats of Healthy People, Bull. Johns Hopkins Hosp. **32**:33, 1921.

49. Bachr, Shwartzman and Greenspan.[3] Belk.[36a]

it induces a serious pulmonary pathological state which, in the days before specific therapy, carried a high mortality rate. The importance of the isolation of the organism lies in the availability of effective chemotherapeutic and antibiotic agents.

MENINGITIS

Meningitis constitutes a prominent manifestation of extrapulmonary Friedländer-aerogenes infection, although the organism is one of the less frequently encountered pathogens in this disease.[50] In 1931, Rothschild [51] reported the disease in an adult following otitis media and mastoiditis. Recovery ensued after mastoidectomy and surgical drainage of an associated subdural abscess. His was the second case to be reported in the American literature and the first case in which recovery occurred. Fothergill and Sweet,[52] in a survey of 705 cases of meningitis observed over a 12 year period at the Boston Children's Hospital, found one caused by the Friedländer bacillus, an incidence of 0.14 per cent. The patient was a 4 week old infant who had had vomiting and diarrhea since the age of 3 days.

Ransmeier and Major [53] described a fatal case in an adult in whom multiple small intestinal ulcerations were found. Although no mention was made of antemortem or postmortem stool cultures, they postulated that the infection may have begun as an enteritis with subsequent blood stream invasion and meningeal localization. In their review of the literature they included 29 additional cases of Friedländer meningitis, of which 11 occurred in children. None of the children was older than 3 years, and nine were under 9 months of age. Only one of the children recovered, and he was treated with sulfapyridine. In six of the 11 there was no known primary focus. Two had associated pneumonia, and one each otitis, bronchitis and arthritis. In contrast to the children, infections of the middle ear, sinuses and mastoids occurred as foci of entry in over half the adults. Five of the adults had diabetes mellitus, and two of the infants had intracranial hemorrhages. It was the authors' impression that debilitating disease predisposes the patient to the development of meningitis. Included in this series of 30 patients were three in whom the infection was specifically reported as caused by A. aerogenes.

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50. Neal, J. B.: Experience of the Meningitis Division of the New York Department of Health, Am. J. Pub. Health **21**:147, 1931.

51. Rothschild, K.: Meningitis Caused by Friedländer's Bacillus: A Case with Recovery, J. A. M. A. **97**:1956 (Dec. 26) 1931.

52. Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children with Special Reference to Age-Incidence and Bacteriologic Diagnosis, J. Pediat. **2**:696, 1933.

53. Ransmeier, J. C., and Major, J. W.: Friedländer's Bacillus Septicemia and Meningitis: Report of Case and Autopsy, with Analysis of 29 Cases Collected from Literature, Arch. Int. Med. **72**:319 (Sept.) 1943.

Since publication of the paper by Ransmeier and Major, sporadic cases have been reported by others.[54] Jacob and Top[55] have reported 7 cases of Friedländer meningitis in adults. The two who survived had negative blood cultures. Of the five patients who died, blood cultures were drawn from four and were positive in three. The ear was the primary focus in five. Diabetes mellitus was present in two. Their experience parallels the report of Ransmeier and Major, who were able to find records of blood cultures in only 10 of the 30 patients they reported. In five, the blood culture was positive, and all these patients died. Of the five who had negative blood cultures, two survived. It would appear from these few examples that bacteremia in the presence of meningitis connotes a graver prognosis than it does in pneumonia.

The total number of infants reported to have recovered is three.[56] Included among our 10 patients was one with meningitis.

CASE 4.—D. D., a 5 week old boy, entered the hospital on Oct. 21, 1948 because of convulsions, generalized weakness and failure to gain weight since the first week of life. The birth weight was 7 pounds (3,175 Gm.). Delivery occurred spontaneously at term after a seven hour labor. No difficulties were encountered immediately after birth except a disinclination on the part of the infant to accept the breast. Jaundice, thought to be physiological, developed on the third day of life. During the first week a low grade fever was thought to have been present, although the temperature was not recorded. At 7 days of age the infant experienced a series of generalized tonic convulsions, one of which is said to have lasted twelve hours. No clonic seizures were noted. He was admitted to another hospital, where he remained for two weeks. After his discharge, severe diarrhea with marked

54. Mori, G. E.: Meningitis a neumobacilo de Friedlander en un niño de veintiseis meses, curada, Rev. Soc. pediat. de Rosario **8**:113, 1943. King, S. J.: Friedländer's Bacillus Meningitis with Report of a Case Treated Unsuccessfully with Sulfadiazine, Ann. Int. Med. **24**:272, 1946. Tartakoff, S.; Grynbaum, B., and LeCompte, P. M.: Friedländer-Bacillus Meningitis Treated with Streptomycin, New England J. Med. **235**:681, 1947. Ghiselin, A. D., and Robertson, R. B.: Friedländer's Bacillus Meningitis Secondary to Otitis Media: A Report of a Case with Recovery and a Review of the Literature, Arch. Otolaryng. **45**:432 (April) 1947. Hough, P. T., and Adelson, L.: Meningitis Caused by Friedländer's Bacillus or Aerobacter Aerogenes: Report of 2 Cases with Autopsies, Am. J. Clin. Path. **17**:534, 1947. Fisher, G. J.: Friedländer's Bacillus Meningitis, Treated in Part with Streptomycin, with Recovery, New York State J. Med. **48**:202, 1948. Daniel, W. A.: B. Mucosus Capsulatus (Friedländer) Meningitis: Recovery of a 3-Week Old Infant with Sulfadiazine and Streptomycin, Pediatrics **3**:3, 1949. Solomon.[9]

55. Jacob, S. S., and Top, F. H.: Friedländer Bacillus Meningitis: Report of 7 Cases with 2 Recoveries, Ann. Int. Med. **28**:1003, 1948.

56. Since this paper was written, Neter, Krauss, Egan and Mason have reported the recovery of a 2 day old infant with meningitis caused by B. aerogenes following aureomycin therapy (Neter, E.; Krauss, H. F.; Egan, G. J., and Mason, T. H.: Aureomycin Treatment of Meningitis Due to Bacillus Pyocyaneus and Bacillus Aerogenes: Report of 2 Cases with Recovery, J. A. M. A. **142**:1335-1337 [April 29] 1950).

pallor and loss of weight developed, and he was readmitted to the same hospital. Several changes of formula were instituted, but he continued to lose weight. A spinal tap is said to have been performed and the fluid described as clear. Following his second discharge two convulsions occurred. During the period prior to his admission to Charity Hospital there were several bouts of vomiting unassociated with the intake of formula. The mother volunteered the information that the child's head had been growing more rapidly than she thought was normal.

Physical Examination.—The temperature was 98.6 F., and the weight was 6 pounds 14 ounces (3,120 Gm.). The head circumference measured 40 cm., and the thoracic circumference was 31.5 cm. The total body length was 80 cm. The patient was poorly nourished and poorly developed with poor skin turgor and evidence of recent weight loss. He appeared chronically but not acutely ill. Respirations were regular but rapid and shallow. The head was disproportionately large and obviously hydrocephalic. Both fontanels were widely patent, and there was marked separation at the sutures. The anterior fontanel measured 8 by 6 cm. and was tense. The pupils reacted sluggishly to light but were equal and regular. Both optic disks were normal. The remainder of the survey, including the neurological examination, yielded essentially normal findings.

Laboratory Data.—The hemoglobin content was 12 Gm., the red blood cell count was 3,310,000 and the white blood cell count was 30,300, with 65 per cent granulocytes, of which 4 per cent were nonsegmented cells, 3 per cent monocytes and 32 per cent lymphocytes. The urine was normal. Results of a serologic test for syphilis and a tuberculin test with old tuberculin (1:1,000) were negative. Serum calcium and phosphorus levels were 10.3 and 4.5 mg. per 100 ml. respectively. Both smear and culture were negative for micro-organisms.

Course.—The patient was entirely afebrile throughout his stay of 9½ weeks in the hospital. On October 24, three days after admission, bilateral subdural taps were done and no hematomas or abscesses were demonstrated. On October 25 a ventriculogram was attempted, and 30 cc. of cloudy xanthochromic fluid was removed from the right ventricle. The opposite ventricle yielded similar fluid, and the air study was abandoned. Examination of the fluid of the right side showed a cell count or 1,200, with a preponderance of polymorphonuclear leukocytes. Protein and glucose were 234 and 58.5 mg. per 100 ml. respectively. Smear of the sediment failed to reveal any micro-organisms. On October 26 the right ventricle was tapped again and a very thick, dark fluid removed. The cell count this time was 20,000, most of the cells being polymorphonuclear leukocytes. Smear of the sediment was again negative, but the culture showed type C K. pneumoniae sensitive to 10 micrograms of streptomycin. Because of the purulent ventricular fluid, penicillin in aqueous solution in a dosage of 10,000 units every 12 hours had been started pending identification of the organism. On isolation of K. pneumoniae streptomycin therapy was initiated in a dosage of 40 mg. every eight hours. Use of penicillin was stopped after eight days. Results of subsequent examinations of the ventricular and spinal fluids are outlined in table 2. A block in the ventricular system was demonstrated by the injection of 1 cc. of phenolsulfonphthalein into the right ventricle, with failure to recover the dye either in the left ventricle or in the spinal fluid. On another attempt, the dye was injected into the spinal fluid and could not subsequently be recovered in either ventricle. On November 4 type C K. pneumoniae was again isolated from both ventricles. All subsequent ventricular and spinal fluid cultures were sterile.

Except for a slow gain in weight up to 9 pounds 11 ounces (4,385 Gm.), the patient's general condition remained essentially unchanged. The head circumference increased to 45 cm. The ventricular fluid gradually became clear, and the

cell count fell to 150, with 90 per cent lymphocytes. Lumbar puncture prior to discharge showed the fluid to be clear and under increased pressure, with 12 lymphocytes per cubic millimeter and 228 mg. of protein per 100 ml. Several attempts at ventriculography were unsuccessful. Streptomycin treatment was discontinued on December 12, and the patient was discharged. He was followed in the clinic for the next three months. His weight rose to 19 pounds (8,620 Gm.) and he appeared well nourished. The head circumference had increased to 52 cm. and the chest to 43 cm. Hearing and vision appeared intact.

On March 23 the patient was readmitted, because of pneumonia. The temperature was 100.2 F.; he appeared well nourished and well developed and was not

TABLE 2.—*Spinal Fluid Findings in Case 4*

Date	Source	Pressure	Appearance	Cells/Cu. Mm.	Protein	Glucose	Bacteriology
10/21/48	Spinal fluid	100 mm.	Xanthochromic	675 RBC (25% crenated)	504 mg.	66.5 mg.	Smear, negative; culture, Staph. aureus (saprophytic)
10/25/48	Right ventricle	.....	Cloudy, xanthochromic	1,200 (mostly PMN)	234 mg.	58.5 mg.	Smear, negative
10/26/48	Right ventricle	Increased	Thick, cloudy	20,000 (mostly PMN)	Q. N. S.	54 mg.	Smear, negative; culture, K. pneumoniae type C
10/27/48	Right ventricle	Normal (?)	Cloudy	5,040 (90% PMN)	....	....	....
	Left ventricle	Normal	Cloudy	6,400 (90% PMN)	....	....	Culture, K. pneumoniae type C
11/ 4/48	Spinal fluid	.....	Clear, less xanthochromic	180 (mostly PMN)	290 mg.	45 mg.	....
	Right ventricle	.....	Cloudy	5,000 (mostly PMN)	232 mg.	50 mg.	Culture, K. pneumoniae type C
	Left ventricle	.....	Cloudy	2,103 (mostly PMN)	232 mg.	72 mg.	Culture, K. pneumoniae type C
11/12/48	Spinal fluid	.....	Less xanthochromic	35	259 mg.	....	Culture, all negative
	Right ventricle	.....	.....	125	612 mg.	84 mg.	
	Left ventricle	.....	.....	33	576 mg.	90 mg.	
11/19/48	Spinal fluid	.....	Clear, slightly xanthochromic	36 (90% lymph.)	Pandy —	....	Culture, all negative
	Right ventricle	.....	Slightly cloudy	1,007 (90% lymph.)	Pandy 3+	....	
	Left ventricle	.....	Cloudy, slightly xanthochromic	2,933 (79% lymph.)	Pandy 3+	....	
12/13/48	Spinal fluid	Slight increase	Clear	12 lymph.	225 mg.	32 mg.	Culture, negative
3/11/49	Spinal fluid	.....	Clear	No cells	10.1 mg.	....	....
	Ventricle	.....	Clear	5 lymph.	22 mg.	....	....

severely ill. The anterior fontanel was enlarged, measuring 8 by 8 cm. All the sutures were separated, and there was marked craniotabes of the parietal bones. There was proptosis of both eyes, with conjugate deviation to the right. The pupils reacted to light, and the optic disks appeared pale. There was impaired resonance in the left interscapular area with rales at both bases. All deep reflexes were hyperactive. The Babinski sign was negative bilaterally, and there were no paralyses. The blood cell count and the urine were normal. Roentgenogram of the chest revealed an infiltration throughout both lung fields. The roentgenogram of the skull, in addition to the marked enlargement of the cranial vault, showed scattered areas of decreased density surrounded by margins of increased density. Lumbar puncture revealed clear fluid under normal pressure with 5 cells and a protein value of 10 mg. per 100 ml. Ventricular tap likewise demonstrated clear fluid with 5 cells and a protein value of 22 mg. per 100 ml. A ventriculogram revealed marked dilatation of both lateral ventricles, while the third and fourth

ventricles were not visualized. The patient received penicillin, 20,000 units every 12 hours for two days, and sulfadiazine, 1.2 Gm. daily until discharge and made a rapid and uneventful recovery from the pneumonia. He died at home in August 1949 of progressive hydrocephalus.

Summary.—A 5 week old infant was admitted to the hospital because of convulsions, weakness, failure to gain weight and hydrocephalus. The illness dated from the first week of life. Ventricular puncture revealed purulent fluid from which type C K. pneumoniae was grown on several occasions. Streptomycin was administered intramuscularly over a period of six weeks with gradual restoration of the ventricular fluid to normal. During a second admission for pneumonia a pneumoencephalogram showed enlarged lateral ventricles with failure to visualize the third and fourth ventricles, thereby confirming the presence of a block which had been suspected clinically. The hydrocephalus was progressive and the patient died nine months later.

There are two possible explanations for the pathogenesis of the disease in this patient, and it cannot be determined from the available data prior to hospitalization which is the more tenable. The patient may have had congenital hydrocephalus, accounting for his initial neonatal difficulty in adjustment and predisposing to the subsequent development of Friedländer meningitis. The tendency for this disease to occur in debilitated persons was noted by Ransmeier and Major,[55] who cited the cases of two infants with intracranial hemorrhage. On the other hand, it is not inconceivable that the early difficulties were manifestations of the meningitis which caused the hydrocephalus by producing a mechanical block in the ventricular system. That he was afebrile and that he survived a period of four weeks without specific therapy might indicate that (1) virulence of the organism was low and that (2) he was able to achieve some sort of tenuous equilibrium with the pathogen. There can be no question that the cure of the acute meningeal infection is directly attributable to the use of streptomycin.

GENITOURINARY INFECTIONS

Genitourinary disease constitutes a major manifestation of Friedländer-aerogenes infections. Earlier we discussed the recent paper by Wilhelm and his co-workers,[17] who reported a high and apparently increasing incidence of urinary tract disease caused by A. aerogenes. A survey of the relevant publications of the past 20 years indicates that this group of organisms has always been a common urinary tract pathogen, although Campbell [57] found the organism only once as a cause of pyelonephritis in 981 cases of the condition in children. In 1929, Gondolf and

57. Campbell, M. F.: Pediatric Urology, with a Section on Bright's Disease in Infancy and Childhood, by J. D. Lyttle, New York, The Macmillan Company, 1937, vol. I, p. 389.

Stringer [58] reported 50 cases of pyuria due to gram-negative bacilli in which the Bacterium aerogenes was found in 11, or 22 per cent. In the same year, Hill, Seidman, Stadnichenko and Ellis [59] analyzed 200 cases in which gram-negative bacilli were isolated from the urine. In 79 the organism was described as belonging to the genus Aerobacter, and in 12 of these the patients had bacteremia. In the series of Lévy-Bruhl and Viala [60] four of the 67 patients, 6 per cent, had pyuria due to the Friedländer bacillus. These authors regard the urinary tract as the most frequent site of disease following blood stream invasion by the organism, localization being facilitated by anatomic malformation. All gradations of severity of the pathological process may be encountered, and the organism may establish itself in any part of the urinary tract.

The reports by Baehr and his colleagues [5] and Swartz and Rhode [6] also indicated a high incidence of anatomic anomalies in urinary infections caused by the Friedländer-aerogenes group. Many instances of infections with these organisms are mixed, and the organisms occur together with E. coli and members of the Proteus group.[61]

The disease of one of our 10 patients belongs in the category of genitourinary infection.

Case 5.—G. P., an infant boy, was delivered on Oct. 2, 1949, at Charity Hospital, spontaneously and without incident, at term, of a seronegative primigravida after an eleven hour labor. The birth weight was 7 pounds 10 ounces (3,460 Gm.). At birth the infant was pale, had a slightly yellow tint to the skin and presented the classic features of mongolism. Within eight hours it was apparent that the jaundice was increasing, and by the next day his color was a deep orange-yellow. He passed normal meconium stools, and the urine was yellow. The only additional finding on examination was the presence of a harsh systolic murmur over the entire precordium.

The hemoglobin content was 18.5 Gm.; red blood cell count, 6,000,000, and white blood cell count, 14,300, with 49 per cent granulocytes, 45 per cent lymphocytes and 6 per cent monocytes. The infant's blood was type A, Rh positive; the mother's, type O, Rh positive. The maternal blood was not examined for anti-A agglutinins. Because of the possibility of neonatal sepsis, the patient was given 20,000 units of penicillin every eight hours. Culture of blood drawn before therapy was begun was sterile. The patient made an adequate weight gain and was discharged after four days, still jaundiced. The icterus was thought to be physiological.

58. Gondolf, H. J., and Stringer, M. S.: A Bacteriological Study of the Gram Negative Bacilli Found in 50 Cases of Infection of the Urinary Tract, New Orleans M. & S. J. **81**:735, 1929.

59. Hill, J. H.; Seidman, L. R.; Stadnichenko, A. M. S., and Ellis, M. G.: A Study of 200 Cultures of Gram-Negative Bacilli Isolated from Cases of Genito-Urinary Infection, J. Bact. **17**:205, 1929.

60. Lévy-Bruhl, M., and Viala, M.: Sur les infections génito-urinaires à pneumobacille de Friedländer, J. d'urol. **39**:193, 1935.

61. Sandholzer, L. A., and Scott, W. W.: A Bacteriological and Clinical Study of Bacillary Infections of the Urogenital Tract, J. Urol. **42**:183, 1939.

The patient was readmitted at the age of 15 days. The jaundice had persisted unchanged. His general condition had been good, but a mild diarrhea made its appearance one day before admission. At this time it was revealed that for a period of four months during the fall of 1948 the mother had had jaundice, which, however, had subsided clinically before conception. Physical examination of the infant revealed, in addition to mild dehydration, only the previously noted mongolism, the precordial systolic murmur and moderately intense jaundice. In addition, the liver was palpable 3.5 cm. below the costal margin.

Laboratory studies at this time gave the following results: hemoglobin, 12.2 Gm.; red blood cells, 3,100,000; white blood cells, 9,600, with 54 per cent granulocytes, 36 per cent lymphocytes, 7 per cent myelocytes and 3 per cent metamyelocytes. The blood smear showed no nucleated red blood cells or spherocytes. Red cell fragility in both the patient and his mother was normal. The sedimentation rate by the Wintrobe method was 26 mm. per hour. Result of a serologic test for syphilis was negative. Bile was present in the urine, but urobilinogen was absent. The remainder of the urinalysis gave normal findings. Bile was also present in the stool. The total and direct serum bilirubin values were 22.8 and 11.9 mg. per 100 ml. respectively. The cephalin flocculation test gave a 2+ reaction. Fluoroscopic examination of the heart showed the cardiac contour and size to be within normal limits. The electrocardiogram showed right ventricular preponderance.

The patient remained afebrile throughout the course of his illness except for two occasions toward the end, when the temperature rose to 101 F. Shortly after admission, the dehydration became worse and presented the main challenge to therapy. After an initial respose to the parenteral administration of fluids, the diarrhea recurred, although it was not severe. The patient was almost continuously in acidosis and dehydration despite the administration of blood and fluids, including 5 per cent dextrose in distilled water, isotonic sodium chloride and potassium chloride solutions and sixth-molar sodium lactate. Jaundice became progressively less intense, although it never subsided completely. The total serum bilirubin fell to 3.2 mg. per 100 ml. shortly before death.

By October 31, thirteen days after admission, the patient's condition became critical. The following day he became febrile for the first time and it was apparent that both kidneys were palpably enlarged. The hemoglobin fell to 8 Gm. On November 2, examination of the urine revealed a large number of white blood cells and gram-negative rods. Some pyuria had been recorded six days previously but had been overlooked. A urine culture on November 2 and a culture of blood taken the following day both yielded a pure growth of an organism of the Friedländer-aerogenes group sensitive only to chloramphenicol in vitro. The organism was not tested for its sensitivity to sulfadiazine. The blood urea nitrogen at this time was 38 mg. per 100 ml. A lumbar puncture was performed on November 2 because of the presence of a bulging fontanel. The spinal fluid was clear; the protein content was 63 mg. per 100 ml., and there were 53 mononuclear cells per cubic millimeter, which were peculiar in that they contained fat globules. It was thought that the spinal fluid changes were probably caused by a cerebral sinus thrombosis.

With demonstration of the pyuria, gram-negative rods on direct smear of the urine and the palpably enlarged kidneys, it was thought that the patient's chief acute difficulty was renal infection probably superimposed on a congenital malformation with sufficient functional impairment to have caused the dehydration and acidosis. Administration of sodium sulfadiazine was instituted intravenously to combat the infection before specific laboratory identification of the organism. The infant appeared to respond to sulfadiazine. The temperature fell to normal,

and the pyuria decreased, although it never disappeared. Two subsequent blood cultures were negative. The blood urea nitrogen fell to 11.6 mg. per 100 ml. After a period of comparative well-being, the patient's condition, deteriorated rapidly, with a recurrence of the diarrhea and dehydration, and he died on November 11.

Autopsy.—The essential pathological observations were limited to the heart and the genitourinary tract. The heart was of normal size and contour, with no significant ventricular hypertrophy. There was dextroposition of the aorta, and the latter showed a marked overriding of a high ventricular septal defect which measured 0.4 cm. The pulmonary artery was hypoplastic and had a bicuspid valve which exhibited fibrinoid degeneration. The ductus arteriosus was obliterated. The right kidney was enlarged and weighed 32 Gm. The left kidney weighed 22 Gm. Hemorrhagic areas were found throughout both kidneys, and the pelves were markedly dilated. Both ureters were moderately dilated, and it was the opinion of the pathologist that folds in the mucosa at the ureteropelvic junction might have caused the obstruction. The anatomic diagnosis of the renal lesion was bilateral hydronephrosis and hydroureter and bilateral pyelonephritis. No explanation is available for the presence of the fat-containing cells in the spinal fluid.

Summary.—The patient, in addition to presenting evidence of mongolism and congenital heart disease, was jaundiced at birth. The blood culture was sterile, and hematological values were normal. There was no Rh incompatibility. The icterus was thought to be physiological, and the patient was discharged on the fourth day. He was readmitted at 15 days of age because of diarrhea, with jaundice still present. The patient presented a continual problem in the maintenance of hydration and acid-base equilibrium. His condition deteriorated despite therapy. His kidneys became palpably enlarged, pyuria appeared and blood and urine cultures were positive for an organism of the Friedländer-aerogenes group. He showed some improvement during treatment with sodium sulfadiazine and the blood culture became negative, but he died after a recurrence of dehydration.

SEPTICEMIA

We have encountered five infants with septicemia. Included among them is one in whom there was an associated genitourinary infection, one in whom there was postmortem evidence of meningitis and three in whom the organism was recovered from the spinal fluid, although no tests for cytological and biochemical evidence of acute meningeal infection were performed. These cases are being considered here rather than in the previous two sections because the bacteriologic localization appeared to be an incident in the general picture of the septicemia and did not play a major role in the illness of any one of the patients.

Mention has already been made of the high incidence of positive blood cultures obtained in patients with Friedländer pneumonia, of the transient nature of the bacteremia and of the absence of any positive correlation between the blood stream invasion and mortality. However, in a disease which at one time carried so high a fatality rate, it may well

be difficult to correlate mortality with any single criterion. Bacteremia is also common in patients with meningitis, in whom it has a serious prognostic significance, but is less frequent in patients with genitourinary disease.

The pathogenesis of Friedländer pneumonia is the same as that of the pneumococcic variety.[62] From an upper respiratory focus bronchogenic dissemination of the organism takes place with bacteremia occurring simultaneously with or secondary to the pulmonary localization. In both meningitis and genitourinary infections, however, the initial phase is probably a bacteremia with secondary implantation in the meninges and urinary tract. It is usually difficult to establish the original source of the organism. Since many of the adults with Friedländer meningitis have had associated otitic infections, it is quite likely that in this disease the organism comes from an upper respiratory focus. In most cases of urinary tract infection, the source is seldom apparent. Although it has been generally assumed that the organism comes from the intestine, most reports make no mention of recovery of the pathogen in stool cultures. Once the meningitis and the urinary infections are established, they may become foci which continue to seed the blood stream. Jobin and Paquet[63] indicated that the sepsis may be so overwhelming as to cause death in 24 to 48 hours without any localization whatever.

Étienne,[40] in his early review of Friedländer infections, cited two cases of septicemia in children, both of whom died. One of these was an infant. Since then the subject of septicemia has been dealt with in the form of case reports in adults which have appeared largely in the French literature. By 1938, Meyer and Amtman[64] had been able to accumulate 104 cases and added one of their own. Few cases have been reported in newborn or older infants. One outbreak in a newborn nursery[65] involved five infants, two of whom died. Diarrhea was the predominant symptom, and all five had positive stool cultures, although in only two was there bacteriologic confirmation of a blood stream involvement. Silverman and Homan[66] have reported the case of a premature infant with A. aerogenes septicemia included among 25 cases

62. Sale, L., Jr., and Wood, W. B., Jr.: Studies on the Mechanism of Recovery in Pneumonia Due to Friedländer's Bacillus: I. The Pathogenesis of Experimental Friedländer's Bacillus Pneumonia, J. Exper. Med. **86**:239, 1947.

63. Jobin, J. B., and Paquet, B.: Septicémie à Friedländer, Laval méd. **3**:151, 1938.

64. Meyer, K. A., and Amtman, L.: Treatment of Friedländer's Septicemia by Sulfapyridine with Recovery, J. A. M. A. **113**:1641 (Oct. 28) 1939.

65. Cass, J. M.: Bacillus Lactis Aerogenes Infection in the Newborn, Lancet **1**:346, 1941.

66. Silverman, W. A., and Homan, W. E.: Sepsis of Obscure Origin in the Newborn, Pediatrics **3**:157, 1949.

of neonatal sepsis, and Levine[67] recently observed that the same organism has been found in the lungs at autopsy of premature infants who died shortly after birth, although no mention was made of blood cultures.

That positive blood cultures may arise in association with foci of infection other than that in the meninges and respiratory and urinary tracts is evident from the case studies of Boettiger, Weinstein and Werne,[4] Jaffe,[68] Norman and Binford[69] and Solomon.[5]

Case 6.—B. G., a 1,470 Gm. premature boy, was born at Charity Hospital on Feb. 20, 1949, after approximately six months' gestation, of a 17 year old seronegative primipara. His condition was poor immediately after birth, but progress was steady after the first 10 days. The birth weight, however, was not regained until the twenty-fifth day. During the sixth week of life his stools became somewhat loose, and by the forty-first day vomiting had developed, the diarrhea had progressed and dehydration and acidosis were present. On a regimen of parenterally administered fluids and blood transfusions with a preliminary period of starvation, the patient made a rather rapid recovery and reestablished a steady weight gain in nine days. His progress was uninterrupted until May 12, at 11 weeks of age, when he was noted to be listless and feeding poorly. On May 16 it was apparent that the patient was jaundiced. Urinalysis on this date showed only large numbers of epithelial cells. On the following day the urine showed a great number of red and white blood cells, and on May 18, in addition to large numbers of cellular elements, the stained sediment of the urine revealed many gram-negative nonmotile rods. Bile was now present in the urine, but urobilinogen was absent. The direct-reacting serum bilirubin was 24.5 mg. and the total bilirubin 30.9 mg. per 100 ml. On this date, daily administration of sodium sulfadiazine, 0.6 Gm. subcutaneously, and streptomycin, 200 mg. intramuscularly, was begun. Blood cultures taken on May 18 and 19 revealed an organism of the Friedländer-aerogenes group. The same organism was grown from the urine in association with a Proteus. The patient's condition grew steadily worse, and paralytic ileus developed, which was combated by continuous gastric suction. Blood and fluids were administered as indicated by the patient's status. Opisthotonus and a moderate degree of spasticity developed, but tension of the fontanel remained normal. The organism was found to be moderately sensitive to both streptomycin and chloramphenicol, and on May 19 intravenous therapy with the latter drug was instituted, a 2.5 per cent solution in propylene glycol being given in a dose of 250 mg. daily. Under combined drug and parenteral fluid therapy improvement was slow but continuous. Use of sodium sulfadiazine was discontinued on May 25, after the patient had received a total dose of 4.05 Gm. On this day blood and urine cultures were negative, and the next day gastric suction was discontinued

67. Levine, S. Z., in discussion on Clifford, S. H.: Prevention and Control of Infection in Nurseries for Premature Infants, Am. J. Dis. Child. **79**:377 (Feb.) 1950.

68. Jaffe, S. A.: Extrapulmonary Klebsiella Pneumoniae Infections: An Analysis of the Literature; Report of 2 Unusual Cases with Recovery, J. A. M .A. **122**:292 (May 29) 1943.

69. Norman, J. K., and Binford, C. H.: Liver Abscess Due to Friedländer's Bacillus (K. Pneumoniae) Complicating Adenocarcinoma of the Ampulla of Vater, Am. J. Clin. Path. **15**:534, 1945.

and oral administration of fluids begun. Intravenous injection of chloramphenicol was stopped because of edema of the scalp secondary to thrombophlebitis, and the drug was given orally until June 4, when use of both streptomycin and chloramphenicol was stopped. The total doses of the two antibiotics were 3.2 and 3.7 Gm. respectively. The jaundice faded slowly, the serum bilirubin returning to normal values on June 23. The infant vomited intermittently until all medications were discontinued. He made a steady gain in weight from a low of 2,160 Gm. to 2,930 Gm. and was discharged on June 28. At no time were any signs of pulmonary infection present.

Ten days after discharge the patient was readmitted with cough, fever and rales in both lung fields. Opisthotonus was still present. Blood, spinal fluid, stool and nose and throat cultures were negative for any pathogens. Because of the etiology of the previous infection and the possibility of a recurrence, administration of streptomycin was started. The temperature fell promptly to normal, and the patient made a rapid recovery, probably uninfluenced by the streptomycin.

Summary.—The patient was a 1,470 Gm. premature infant in whom, while he was still in the nursery, a severe diarrhea with dehydration and acidosis developed at 6 weeks of age. He recovered with standard therapy. His progress was good until 3 months of age, when he became listless and jaundiced. Large numbers of red and white blood cells appeared in the urine. Blood and urine cultures showed a Friedländer-aerogenes organism. Paralytic ileus developed. Therapy consisted in continuous gastric suction and administration of sulfadiazine, streptomycin, chloramphenicol, blood and fluids parenterally. Recovery was slow but progressive.

The septicemia in this instance developed quite insidiously in a premature infant who was well at the time of onset. The nurse in charge of the premature station had remarked for a period of a week that the infant was not doing well; yet physical examination revealed no outward sign of illness until the appearance of jaundice. The occurrence of opisthotonus recalled our first case with pneumonia, that of an infant in whom convulsions, coma and spasticity developed in the course of his disease in the absence of meningitis. The positive urine culture and the presence of red and white blood cells in the urine probably represent manifestations of renal infection as described by Baehr and his colleagues, and a genitourinary investigation will be necessary to exclude the presence of a congenital malformation. Specific therapy in this instance included administration of sulfadiazine, streptomycin and chloramphenicol. The two former agents are known to be effective against the Friedländer-aerogenes group, and the latter was found to be moderately effective in vitro. We regard the sepsis as the primary disease with urinary infection occurring secondary to the blood stream invasion.

Case 7.—J. M., a 3 week old girl, was admitted to Charity Hospital on April 14, 1949 because of vomiting and diarrhea. Labor occurred at term, and delivery was normal. There were no neonatal complications except for the development of thrush, which cleared with local therapy. Subsequent to delivery, the

infant was cared for in an institution. At 10 days of age a right inguinal hernia was noted. Three days later a rather severe erythema of the vulva and buttocks appeared, and the patient received 75,000 units of penicillin daily, together with magnesium sulfate soaks to the affected parts. It soon became apparent that the patient was having a moderately severe diarrhea, and when vomiting ensued, one day prior to admission, hospitalization was sought.

Physical Examination.—The patient was a poorly nourished, poorly developed infant girl, not severely ill but with evidence of recent weight loss. The temperature was 99.2 F. There appeared to be very little subcutaneous fat, and the skin turgor was poor. The anterior fontanel was slightly depressed. The only other abnormalities of note were an easily reducible right inguinal hernia and some excoriation of the buttocks.

Laboratory Data.—The red blood cell count was 5,320,000. The white blood cell count was 12,000, with 56 per cent granulocytes (23 per cent nonsegmented) and 44 per cent lymphocytes. The results of urinalysis were normal. The serologic reaction for syphilis was negative. A blood culture on admission was negative. Nose and throat culture revealed beta hemolytic Streptococcus, Escherichia and Staphylococcus albus. A stool culture on admission and one taken one day prior to death were both negative for any pathogens. A roentgenogram of the chest was negative.

Course.—Soon after admission the patient passed a number of explosive watery stools. She became listless and pale, and her cry was weak. She was placed on a regimen of starvation, parenterally administered fluids and blood transfusions. She made a gradual recovery, and by May 2 was receiving small feedings of a half-skimmed milk mixture containing 10 per cent carbohydrate. At this time an abscess was noted over the right thigh, and 20,000 units of penicillin was administered intramuscularly every six hours. On May 5 the abscess was drained, and Staph. aureus was cultured. On May 9 the abscess was fully healed and the diarrhea arrested, and penicillin therapy was discontinued. On the next day there was a recurrence of the diarrhea with vomiting and dehydration. The carbon dioxide content was 15.2 millimoles per liter, and the chloride, 104 milliequivalents per liter. Oral feedings were discontinued and parenteral fluid administration resumed. On May 12 use of penicillin was again started, 20,000 units intramuscularly every 12 hours. By May 14 the infant was able to take small amounts of oral feedings, but from this point her condition deteriorated rapidly. On May 15 her temperature rose to 101 F., after having been normal since admission. On the following day she was noted to be jaundiced. The scalp, at the site of the intravenous administration, was edematous and discolored. There was some periorbital edema. The liver was palpable 3 cm. below the costal margin. The dose of penicillin was increased to 10,000 units every three hours. A nose and throat culture at this time revealed bacilli of the Friedländer-aerogenes group in addition to a Streptococcus of the viridans group and Staph. albus. The patient gave no evidence of any response to therapy, and she died on May 17. Cultures of the heart blood and spinal fluid immediately after death both revealed a heavy growth of an organism of the Friedländer-aerogenes group. Permission for autopsy was denied.

Summary.—A 3 week old infant was admitted because of vomiting and diarrhea. The blood culture on admission was sterile. The patient made a good response to a regimen of starvation, parenterally administered fluids and transfusion, but then a relapse occurred. Jaundice appeared, and the patient's course was progressively downhill until she

died. Shortly before death a throat culture revealed some Friedländer-aerogenes organisms in addition to a hemolytic Streptococcus and Staph. albus. Postmortem culture of the blood and spinal fluid revealed a heavy growth of the Friedländer-aerogenes organism in both.

CASE 8.—J. R., a premature boy, was admitted to the Charity Hospital on Dec. 12, 1948, at the age of 2 days, because of "failure to eat." The birth weight was 3 pounds 12 ounces (1,647 Gm.). It was the mother's first pregnancy, and the total duration of gestation was 7½ months, with the expected date of confinement Jan. 28, 1949. She had received antepartum care, but the result of her serologic test for syphilis was not known. Labor was prolonged, and the membranes had ruptured spontaneously three hours before delivery, which had occurred at another institution. The patient remained in an incubator under oxygen until his removal to this hospital. Two subcutaneous clyses of 5 per cent dextrose in distilled water had been given in unknown amounts.

Physical Examination.—The general condition of the infant was poor, and he was not weighed on admission. The temperature was 100.2 F. There were numerous areas of erythema over the skin, probably representing burns, since the infant had been surrounded by hot water bottles in transit. Respirations were irregular and shallow. Thoracic expansion was decreased, and there was a definite lag on the right side. There was some flaring of the alae nasi. Resonance was decreased over the entire left side of the chest, and the breath sounds were obscured by many fine and coarse rales heard bilaterally. The heart presented no abnormal findings. The abdomen was distended, and no viscera or masses were palpable.

Course.—A diagnosis of atelectasis or pneumonia or both was made, and therapy with 10,000 units of penicillin administered intramuscularly every three hours was begun. He was placed in an incubator under oxygen. Despite therapy, his course went rapidly downhill. Respirations became gasping with prolonged periods of apnea, and he died in one of these episodes of apnea seven hours after admission. Permission for autopsy was not obtained. Material taken for bacteriologic study immediately on death gave the following results: Nose and throat cultures revealed Pseudomonas aeruginosa; the blood culture was sterile, and the spinal fluid yielded a pure culture of an organism of the Friedländer-aerogenes group.

Despite the failure to recover the bacillus from the blood, we regard the presence of the organism in the spinal fluid as a consequence of prior blood stream invasion. It would be difficult to determine whether death was related to the complications of prematurity or to overwhelming sepsis.

CASE 9.—V. D., a premature girl, was born at Charity Hospital on March 31, 1949 of a primigravida after an approximately six months' gestation. Delivery was spontaneous, aided by an episiotomy. Because of the infant's very poor condition she was not weighed immediately. Her cry was weak, but there were no obvious abnormalities. After the administration of 2.4 mg. of vitamin K she was placed in an incubator under oxygen. On the following morning her weight was 780 Gm. Gavage feedings were begun on the second day, but the infant continued to do poorly. She regurgitated a great deal and had several bouts of cyanosis. Death occurred on the fourth day. Cisternal fluid taken immediately on death was grossly bloody. Cultures of the blood and cerebrospinal fluid, also taken immedi-

ately on death, revealed the presence of an organism of the Friedländer-aerogenes group and a paracolon bacillus. Autopsy revealed intraventricular, subdural and extradural hemorrhage and bilateral atelectasis.

Case 10.—B. W. was born at Charity Hospital on July 23, 1949 of a seronegative primipara after an uneventful pregnancy. Delivery at term was uncomplicated and accomplished by low forceps extraction with episiotomy. The birth weight was 6 pounds 15 ounces (3,150 Gm.). Results of physical examination were entirely normal. The infant was placed on the nursery routine, which called for a preliminary period of nothing by mouth for 12 hours, after which time he was placed at breast. Approximately 40 hours after birth the patient vomited some greenish fluid. It was noted that he had passed no meconium stools since birth. Physical examination revealed no other abnormality than marked abdominal distention with visible peristalsis. A roentgenogram of the abdomen in the erect position revealed distended loops of bowel with fluid levels. A saline enema yielded no meconium return. Continuous Wangensteen suction was instituted and fluids administered intravenously for several hours prior to surgery. Abdominal laparotomy revealed an atresia of the large bowel at the junction of the descending colon and the sigmoid, and a colostomy was performed. During operation a tear was made inadvertently in the mesentery of the cecum. The latter became severely discolored and was exteriorized. The following day a portion of the exteriorized cecum was resected.

During the three weeks that the patient survived his temperature was consistently elevated between 100 and 103 F. Large amounts of fluid were lost via the cecostomy, and the patient was given corresponding amounts of blood, casein hydrolysate, isotonic saline solution and 5 per cent dextrose in distilled water. Except for an initial low value for blood carbon dioxide-combining power and a high value for blood chloride, all subsequent determinations were within the normal range. On August 1 the patient was considered sufficiently well to be started on oral feedings of evaporated milk. On August 4 an extraperitoneal closure of the cecostomy was done. At the same time an abscess of the scalp was discovered and incised. Culture of the pus revealed an organism of the Friedländer-aerogenes group. On the following day the patient became distended again and suction was reinstituted. By August 6 he was jaundiced and it was apparent that his condition had deteriorated. Jaundice became progressively deeper, and the bleeding time was one hour. Direct serum bilirubin was 10.7 and total serum bilirubin was 26.5 mg. per 100 ml. respectively. At this time thrombophlebitis of the scalp veins appeared at the sites of the infusions and the patient became edematous. On August 10 the cecostomy reopened spontaneously and drained. By August 11 left-sided convulsive twitchings had developed with deviation of the eyes to the left. His course was progressively downhill, and he died on August 13. Blood cultures taken on August 8, 9, 12 and 13 all revealed a gram-negative encapsulated rod similar to the Friedländer-aerogenes organism isolated from the scalp abscess. One culture also contained a hemolytic Streptococcus and another a Proteus. The Friedländer-aerogenes organism was resistant to streptomycin.

During the course of the patient's illness he was treated with penicillin, streptomycin, sodium sulfadiazine, sulfadiazine, aureomycin and chloramphenicol, all in adequate dosage, but to no avail.

Autopsy was performed 24 hours after death. The final anatomic diagnoses were (1) atresia of the sigmoid colon, (2) postoperative colostomy and cecostomy, (3) peritonitis, (4) meningitis, (5) pneumonia, (6) atelectasis of the left lung, (7) infarction of the right lung and (8) adrenal hemorrhage. The meningitis consisted of a purulent exudate over the parietal lobe on the right extending down

over the temporal lobe. The liver was stained with bile but both grossly and microscopically gave no evidence that it was the cause of the jaundice. Autopsy cultures were badly contaminated and therefore unsatisfactory.

Summary.—This patient was a full term infant who manifested signs of intestinal obstruction 40 hours after birth. Laparotomy revealed an atresia of the colon necessitating a colostomy. During the operation the mesentery of the cecum was accidentally injured, necessitating exteriorization with subsequent resection. A scalp abscess appeared, and culture of the pus revealed an organism of the Friedländer-aerogenes group. Four blood cultures were positive for the same organism. The patient died despite the use of penicillin, streptomycin, sulfadiazine, aureomycin and chloramphenicol.

In five patients septicemia developed in the newborn period or shortly thereafter, and four of these died. Three of these five were premature infants. Of these, only one survived while the other two died at 2½ and four days of age, one with signs and symptoms of respiratory difficulty and the other with an extensive intracranial hemorrhage. Of the two patients who succumbed, one was seriously debilitated by a severe preexisting diarrhea and the other by surgical complications attendant on repair of an atresia of the colon. The latter had pathological evidence of meningitis at autopsy. It would appear from this very small series that Friedländer-aerogenes infections are more likely to occur in those infants who are debilitated by disease or the handicaps of prematurity. The sole survivor among the five appeared well at the time of the onset of the infection.

In the three patients who did not succumb at once jaundice developed. It was probably a manifestation of the sepsis, yet it is interesting to recall that patients with biliary disease formed a large percentage of the series of Baehr and his colleagues [2] and that seven of Solomon's patients with pneumonia were jaundiced.[3c4]

Positive antemortem blood cultures were obtained in two cases. In a third, an antemortem throat culture revealed the organism but the blood culture was negative. However, culture of the blood and spinal fluid immediately on death were both positive. In the remaining two patients no antemortem cultures were carried out, but the organism was recovered from the spinal fluid in one and from the blood and spinal fluid of the other immediately on death. Death of these two infants was due primarily to the complications of prematurity. Baehr, Shwartzman and Greenspan have expressed the belief that postmortem cultures which reveal the Friedländer bacillus are not entirely valid diagnostic criteria because of the tendency to preagonal invasion and postmortem contamination. Perlman and Bullowa,[3c8] on the other hand, never found the organism in hundreds of preagonal and postmortem cultures from patients who did not have Friedländer infections. We are

of the opinion that all five patients represent instances of Friedländer-aerogenes septicemia, although the clinical picture was dominated severally by the presence of an intracranial hemorrhage, by respiratory difficulty, by diarrhea and by the complications attendant on the surgical repair of intestinal atresia.

TREATMENT

The therapeutic assault on the Friedländer bacillus has gone through much of the same evolution as that against the Pneumococcus. Bullowa, Chess and Friedman [25] used type A Friedländer anti-serum in a small series of patients with pneumonia and reported a low mortality. In contrast, five of 32 of Solomon's patients [26d] and 13 of 37 treated by Perlman and Bullowa [26g] died despite serum therapy. Experimental trials with sulfanilamide indicated little if any effect,[70] although Solomon reported the recovery with this drug of one patient with chronic pulmonary disease.[26e] Sulfapyridine was regarded as not significantly more effective than sulfanilamide in experimentally induced infections in mice,[71] yet four patients with chronic pneumonia in Solomon's series recovered with sulfapyridine.[26e] Feinstone and his co-workers [72] were able to demonstrate that sulfadiazine had a striking therapeutic effect as measured by the survival rate in mice of 73 per cent as against 6 per cent with sulfapyridine. Trevett, Nelson and Long [73] reported good results with this agent in a patient with a urinary tract infection and stated that Hodes had effected a cure of Friedländer meningitis with the same drug. On the other hand, only one of Grotts' seven infants with pneumonia showed any response to sulfadiazine.[18] In our experience, sulfadiazine was curative in one patient with pneumonia with a positive blood culture, and, while the patient with pyelonephritis eventually succumbed to the infection, it was considerably ameliorated by the sulfadiazine.

This group of organisms is not ordinarily regarded as being susceptible to penicillin, although Kobacker and Mehlin [74] have described a

70. Kolmer, J. A., and Rule, A. M.: Sulfanilamide and Sulfapyridine in Treatment of Experimental B. Friedländer (Klebsiella Pneumoniae) Infections of Mice, Proc. Soc. Exper. Biol. & Med. **42**:305, 1939.

71. Bliss, E. A.; Feinstone, W. H.; Garrett, A. W., and Long, P. H.: Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary, and Friedländer's Bacillary Infections in Mice, Proc. Soc. Exper. Biol. & Med. **40**:619, 1939. Kolmer and Rule.[70]

72. Feinstone, W. H.; Williams, R. D.; Wolff, R. T.; Huntington, E., and Crossley, M. L.: The Toxicity, Absorption, and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine), Bull. Johns Hopkins Hosp. **67**:427, 1940.

73. Trevett, G. I.; Nelson, R. A., and Long, P. H.: Studies on Sulfadiazine: II. The Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections, Other Than Pneumonia, Bull. Johns Hopkins Hosp. **69**:303, 1941.

74. Kobacker, J. L., and Mehlin, G. B.: Klebsiella Pneumoniae Bacteremia Successfully Treated by Penicillin, Am. J. M. Sc. **210**:66, 1945.

case of K. pneumoniae bacteremia secondary to a peritonsillar abscess with recovery after use of penicillin. No in vitro sensitivity studies were done. Grotts' experience with this agent was uniformly unsatisfactory,[15] and two of our three patients with pneumonia did not respond until streptomycin in one case and streptomycin and aureomycin in the other were administered.

Heilman[75] recently demonstrated the efficacy of streptomycin against experimental infections, and Herrell and Nichols[76] found it effective against urinary infections and tracheobronchial suppuration caused by this group of organisms. We have encountered few clinical reports in which aureomycin and chloramphenicol have been used, but Schoenbach[77] has indicated that the two antibiotics have the same order of activity in vitro. Their minimal inhibitory concentration against the Friedländer-aerogenes group was in the range of 1.25 to 5 micrograms per milliliter. Both are said to be less effective than polymyxin D, which has a minimal inhibitory concentration against the same group of organisms of 0.312 to 1.25 micrograms per milliliter.

Wilhelm and his colleagues[17] recently used aureomycin successfully in treatment of genitourinary infections. In a series of 50 cases the immediate clinical response was good in 42 (84 per cent). However, the incidence of recurrence was 43 per cent, and in some cases the recurrence took place as long as two months after the cessation of aureomycin therapy. Readministration of the antibiotic resulted in sterilization of the urine in most of the patients with recurrence. The authors felt that the action of aureomycin was bacteriostatic rather than bactericidal.

The resistance of the pneumonic infection to treatment may possibly be explained by the work of Smith and Wood.[78] They have indicated that phagocytosis, which occurs in the absence of any demonstrable antibody titer, is a surface phenomenon by which the organisms are trapped against the alveolar wall. Destruction of the latter by necrosis may deprive the phagocytes of a surface on which to operate, and the low oxygen tension prevailing within the abscesses may reduce the phagocytic power of the leukocytes.

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75. Heilman, F. R.: Streptomycin in the Treatment of Experimental Infections with Micro-Organisms of the Friedländer Group (Klebsiella), Proc. Staff Meet., Mayo Clin. **20**:33, 1945.

76. Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A Study of 45 Cases, Proc. Staff Meet., Mayo Clin. **20**:449, 1945.

77. Schoenbach, E. B.: The Newer Antibiotics: Polymyxin, Chloromycetin, and Aureomycin, J. Mt. Sinai Hosp. **16**:71, 1949.

78. Smith, M. R., and Wood, W. B., Jr.: Studies on the Mechanism of Recovery in Pneumonia Due to Friedländer's Bacillus: III. The Role of "Surface Phagocytosis" in the Destruction of the Micro-Organisms in the Lung, J. Exper. Med. **86**:257, 1947.

So far as therapy is concerned, it is suggested that on the isolation of an organism of the Friedländer-aerogenes group streptomycin be administered. In vitro studies should be performed to determine whether either aureomycin or chloramphenicol might be more effective than streptomycin.

SUMMARY

Because infections caused by the Friedländer-aerogenes group of organisms are infrequent in children, we have recorded 10 cases, all of infants, in which these organisms were encountered as pathogens. Included are three cases of pneumonia, one of meningitis, one of pyelonephritis and five cases of septicemia, in three of which no localization was apparent.

While the reported incidence of Friedländer-aerogenes infections is low, more exact bacteriologic determinations with the use of capsular staining might reveal a higher incidence. The growing number of cases reported recently may indicate that an actual increase in these infections is taking place. This may in part be accounted for by the widespread use of penicillin and the occurrence of superinfections as a consequence. Elimination of susceptible gram-positive flora by the penicillin in some instances permits invasion of the body by resistant gram-negative bacilli.

Because A. Aerogenes and the Friedländer bacillus have similar morphological, cultural, biochemical and serologic characteristics and because no valid criteria for their differentiation have been established, we are considering them as a single group. They are distributed widely in nature, and the main sites of normal habitat in man are the intestine and, less commonly, the respiratory tract.

The diseases most commonly caused by these organisms are pneumonia, genitourinary infections, meningitis and septicemia. Pathological localization may, however, occur in any part of the body.

While Friedländer pneumonia occurs in adults in acute and chronic forms, the chronic phase has been encountered in childhood only once. All instances of pneumonia reported in children have been in infants, and the mortality in this age group is lower than in adults. Bacteremia occurs in a large proportion of patients but appears to be transient and unrelated to prognosis. Clinically the disease is indistinguishable from other bacterial pneumonias and is identified only by the isolation of the organism from the blood or from the pharynx in pure or predominant growth. Lack of response to penicillin, recovery with streptomycin and disappearance of the organisms from the pharynx are additional factors which may aid in the differential diagnosis. All three of our patients with pneumonia recovered, one on sulfadiazine, one on streptomycin after failure of penicillin, and the third on streptomycin and aureomycin after failure of penicillin and sulfadiazine.

Meningitis is less frequent than pneumonia. While in adults it occurs commonly as a consequence of otitic infection, in children there is seldom evidence of a preceding focus. In this disease bacteremia has a more serious prognostic significance. Debility appears to predispose to the development of meningitis. Previously only three infants have been reported to have survived. We have recorded a single instance of type C Friedländer meningitis in a 5 week old infant who recovered after prolonged treatment with streptomycin only to succumb nine months later as a result of progressive hydrocephalus. It was not clear whether the meningitis was the cause of the hydrocephalus or whether the latter antedated the infection.

Friedländer-aerogenes organisms are frequently encountered in genitourinary disease. In addition to pyelonephritis, one patient had mongolism and congenital heart disease. No fully defined anatomic malformation, which many believe predisposes to infection with this organism, was demonstrable. Death occurred as a result of dehydration which was unresponsive to therapy.

Five of our patients had septicemia. In all, the disease appeared in the newborn period or shortly thereafter. Three were premature infants. The four who died were all debilitated by preexisting disease. In three jaundice developed. While positive blood cultures are common in patients with pneumonia, meningitis and pyelonephritis, sepsis has not been commonly reported in the absence of any localization of the organism.

Of the sulfonamides, sulfadiazine alone appears to have therapeutic usefulness. Of the newer antibiotics, streptomycin has had the widest trial and is usually a very effective drug. Aureomycin and chloramphenicol have had limited clinical trial to date but appear to be as effective as streptomycin. It is suggested that streptomycin therapy be instituted on isolation of the organism and that in vitro sensitivity studies be performed to determine whether either aureomycin or chloramphenicol has greater antibiotic potency.

News and Comment

ANNOUNCEMENTS

The Tulane University of Louisiana School of Medicine, division of Graduate Medicine, is again offering a short continuation course in pediatrics (for specialists), February 12 to February 17, Dr. Ralph V. Platou, chairman. This course consists of clinical presentations followed by seminar discussions which will emphasize the application of the fundamental medical sciences to the practice of pediatrics.

GENERAL NEWS

Specialists Certified by American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., after examinations in San Francisco on June 30 and July 1 and 2, 1950:

George E. M. Adkins, Seattle; John R. Almklov, Bakersfield, Calif.; Hilton B. Atherton, San Francisco; Junius Ernest Atkins, Jr., San Francisco; Landon H. Bachman, Millbrae, Calif.; Philip A. Bearg, San Luis Obispo, Calif.; Paul Frederick Betzold, Seattle; Elizabeth Jane Bradley, San Mateo, Calif.; William McClelland Brownlee, San Diego, Calif.; Henry B. Bruyn, Jr., San Francisco; Walter R. Buerger, Long Beach, Calif.; Richard Ames Colley, Studio City, Calif.; George Nino Dannell, North Hollywood, Calif.; Alfred J. Fisher, San Francisco; James Hartwell Flippen, Jr., Redwood City, Calif.; Mitchell L. Frank, Los Angeles; Paul R. Freeman, Redwood City, Calif.; David Belais Friedman, Oakland, Calif.; Gordon E. Gibbs, Baltimore; Herbert Greenhood, San Francisco; Barbara Cutting Halpern, Beverly Hills, Calif.; Oscar Herz, San Francisco; Carl A. Holmes, Pheonix, Ariz.; Lacy George Horn, Jr., Vicksburg, Miss.; Deron Hovsepian, Pasadena, Calif.; Dean L. Hyde, Fresno, Calif.; Eugene L. Ireland, Santa Monica, Calif.; Herbert Livingston Kehr, Beverly Hills, Calif.; Clifford K. Kobayashi, Honolulu, T. H.; Fremont P. Koch, Temple City, Calif.; Neil N. Litman, Inglewood, Calif.; William J. Miller, Eugene, Ore.; Percy Minden North Hollywood, Calif.; Floyd Albert Miracle, Napa, Calif.; Edwin Albert Moody, Bend, Ore.; Jerry Newton, San Antonio, Texas; Beulah Parker, Berkeley, Calif.; John Holmes Peyton, Honolulu, T. H.; Naomi Kime Pitman, Los Angeles; Elizabeth Lodge Rees, Berkeley, Calif.; David Rottapel, North Hollywood, Calif.; Paul Rousseau, Oakland, Calif.; Joseph A. Schaefer, Portland, Ore.; Karl William Schmidt, Burbank, Calif.; Monte Schwartz, Alhambra, Calif.; John Green Scott, Reno, Nev.; Maynard C. Shiffer, Salem, Ore.; Henry K. Silver, San Francisco; Richard L. Sleeter, Medford, Ore.; Harold I. Tarre, Long Beach, Calif.; John Girdwood Thom, Los Angeles; Roger Hal Wakefield, Provo, Utah; Standish John Watson, Walnut Creek, Calif.; Katherine E. White, Long Beach, Calif.; William Henry Wilson, San Bernardino, Calif.; Martin Sanford Withers, Los Alamos, N. M.; Stanley Willard Wright, Berkeley, Calif.; Stephen Z. M. Voong, Princeton, N. J.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

A Naturally Fortified Milk Modifier: I. Laboratory Studies of Apple Syrup as a Carbohydrate for Infant Feeding. Bernhard Spur, Sarah Bushong and Irving Wolman, J. Pediat. **36**:588 (May) 1950.

Apple syrup, concentrated apple juice, contains, in addition to levulose, dextrose and sucrose, small amounts of vitamin C (30 mg. per hundred milliliters). It also contains iron (10 mg. per 100 cc.) and pectin (0.02 to 0.5 per cent). At room temperature, about 33 per cent of vitamin C is lost in a six month period. At refrigerator temperature, the loss is about 25 per cent. In test animals, the iron is readily available for hemoglobin formation. The pectin content of this product has been standardized at 0.5 per cent by the addition of measured amounts.

Macdonald, Pittsburgh.

A Naturally Fortified Milk Modifier: II. Clinical Studies of Apple Syrup As a Carbohydrate for Infant Feeding. I. Wolman, B. Dickstein, J. Jones, B. Spur, J. Githens, R. Nicholas and C. Christensen, J. Pediat. **36**:594 (May) 1950.

Partially neutralized apple syrup with added pectin is a satisfactory milk modifier for infant feeding. It is usually well tolerated and mixes easily, even with cold milk. It may have a laxative action in some infants and should be given in small amounts when there is a tendency for the infant to form loose stools. Anemic children seem to improve on apple syrup, presumably because of its available iron.

Macdonald, Pittsburgh.

Postprandial Lipemic Response in Infants and Children. W. Robert Elghammer, John M. Reichert and Herbert F. Philipsborn Jr., Pediatrics **5**:621 (April) 1950.

The chylomicrogram is a simple and time-saving means of serially determining neutral blood lipid levels. It is of value in studying chronic intestinal indigestion. The clinical significance of the chylomicrogram is equal to that of the vitamin A curve. The advantages of the chylomicrogram over the vitamin A curve are its simplicity, rapidity and availability and its use of capillary blood specimens.

Relation of the Let-Down Reflex to the Ability to Breast Feed. Niles Rumely Newton and Michael Newton, Pediatries **5**:726 (April) 1950.

The existence and function of the let-down reflex was studied in 103 mothers who fed their babies at the breast while in hospital after delivery. Successful breast feeders reported a significantly higher incidence of symptoms of let-down than unsuccessful breast feeders. Successful breast feeders made a significantly higher proportion of their milk available to the baby and the breast pump before let-down was artificially induced with alpha hypophamine. The let-down reflex functioned more erratically in the unsuccessful breast feeders. Methods by which the let-down reflex might be helped to function more adequately are discussed.

CALCIUM METABOLISM AND ITS PART IN CLINICAL PEDIATRICS. K. N. SUKHTHANKAR, Indian J. Pediat. **17**:12 (Jan.) 1950.

Calcium metabolism and its practical significance are breifly described.

McGUIGAN, Evanston, Ill.

PHARMACOLOGIC TESTS WITH BONE MEAL: (1) ELECTROCARDIOGRAMS, (2) BASAL METABOLISM, (3) CALCIUM CONTENT OF MILK, (4) GROWTH OF IMMATURE INFANTS. D. GOTTI and P. NICOLAJ, Clin. pediat. **31**: 13 (Jan.) 1949.

A preparation of ground bones of young animals was used in these studies. In children 4 to 11 years of age, 2 Gm. of bone meal administered daily by mouth caused no change in the electrocardiogram and only slight increase in the basal metabolic rate. Ingestion of 2.4 Gm. of bone meal daily caused an increase in the calcium of the milk of nursing mothers from 263 to 288 mg. per milliliter. Giving of bone meal to premature infants directly or to their nursing mothers led to improved weight gains in the infants.

HIGGINS, Boston.

THE N : S RATIO IN HUMAN COLOSTRUM. F. VECCHIO and S. CUTILLO, Pediatria **58**:1 (Jan.) 1950.

The N : S ratio is of value in indicating when colostrum has changed to transition milk and then to milk. The mean N : S ratio in the milk of 10 mothers was 8.7 on the first, 8.9 on the second, 9.6 on the third, 10.0 on the fourth, 10.4 on the fifth and 11.0 on the ninth day of lactation; the mean ratio at later periods was 11.8.

HIGGINS, Boston.

PROBLEMS OF INFANT FEEDING IN BUDAPEST AND THEIR SOLUTION. G. SURANYI, Lattante **20**: 129 (March) 1949.

The infant mortality in Budapest in July and August 1945 was 269 per 1,000; in the corresponding months of 1948, it was 57. In the health campaign to lower this high mortality rate, emphasis was placed on breast feeding. It was observed that the application of short wave therapy to the mother's breasts for 10 treatments increased in one third of the cases the milk excretion in excess of 50 per cent for a prolonged period. Nineteen centers for the collection and dispensing of breast milk have been established in Budapest; as much as 4,166,500 Gm. of breast milk has been collected in one month. This milk has been dispensed to an average of 2,500 infants a month, the premature infant, the infant under 10 weeks and the ill infant receiving preference. The value of this feeding may be judged for one month, when the mortality rate among the babies receiving this breast milk was 36 per 1,000, as against a rate for the city as a whole of 79 per 1,000. The milk was dispensed raw, as it is felt that it has more food value than when pasteurized. Bacteriologic tests for Escherichia coli are made, and no cases of Salmonella infection have been reported. The centers also dispense 14 different infants' formulas and supplementary foods for babies.

HIGGINS, Boston.

MODIFICATION OF THE SPECIFIC DYNAMIC ACTION OF PROTEIN FOLLOWING BLOCK OF THE SYMPATHETIC OR OF THE PARASYMPATHETIC NERVOUS SYSTEM. C. LOMBROSO and C. ARDY, Minerva pediat. **1**: 71 (Feb.) 1949.

These observations were made with dogs. The sympathetic block was obtained with 933F, a derivative of dioxane (Lombroso, C.: *Arch. internat. de pharmaco-*

dyn. et de thérap. **55:** 4, 1937), and the parasympathetic block by atropine. Hydrolyzed casein, was given parenterally and orally and meat and casein were given orally to the animals in three different groups of experiments.

With the parasympathetic block, the oral feedings led to a rise in the respiratory metabolism, whereas the parenteral feeding did not alter the metabolism. With the sympathetic block, the metabolism was found to be lower in each animal after the protein was given.

HIGGINS, Boston.

UTILIZATION IN CHILDREN OF ENZYMATIC HYDROLYSATES OF PROTEIN, GIVEN BY MOUTH AND PARENTERALLY. C. LOMBROSO, L. BUFFONI and C. TADDEI, Minerva Pediat. **2:**37 (Jan.) 1950.

Casein hydrolysates produce the same amount of nitrogen retention and of amino acid excretion in the urine, whether the preparation is given by mouth or intravenously.

HIGGINS, Boston.

KWASHIORKOR (INFANTILE PELLAGRA AND MALIGNANT MALNUTRITION). E. STRANSKY and D. F. DAVIS-LAWAS, Ann. pædiat. **174:**226 (April) 1950.

Kwashiorkor, or malignant malnutrition, is a syndrome due to a deficiency of protein in the food. The characteristic symptoms of the syndrome are hypoproteinemia with reversal of the albumin-globulin ratio in the serum; edema, and a crazy pavement pattern of pigmentation of the skin. Pigmentation and even edema may be absent in moderate cases. The development of the symptoms can be accelerated by diarrhea or any intercurrent debilitating disease. Kwashiorkor is accompanied with symptoms of multiple deficiency, in the first place by symptoms of ariboflavinosis, sometimes A-avitaminosis. Mineral deficiency, due to lack of intake or impairment of absorption, is likewise observed in the syndrome. These deficiencies seem to be accompanying symptoms, not necessarily present in the syndrome. The European *Mehlnährschaden*, a disease due to exclusive feeding with flour soups without milk, corresponds to kwashiorkor, with all secondary deficiencies. The difference is the presence of pigmentations in kwashiorkor and absence in *Mehlnährschaden*. This difference cannot be explained at present. Atrophy of various internal organs, including fatty degeneration of the liver, is a secondary result of any malnutrition. The therapy of kwashiorkor consists in improvement of the hypoproteinemia by parenteral administration of easily digestible amino acids, by which not only the serum protein level but the atrophy and other pathologic changes of the different organs can be beneficially influenced. Administration of vitamins and mineral substances is an adjuvant measure designed to improve as fast as possible an accompanying deficiency. With proper therapy, improvement is possible, even in serious cases. The problem of kwashiorkor gives one the chance to study protein deficiency and its consequences in different combinations, with and without secondary infections and with and without concomitant deficiencies.

FROM THE AUTHORS' SUMMARY.

FOOD REQUIREMENTS AND METABOLISM OF CHILDREN IN SEA CLIMATE. WALTER GOETERS, Med. Klin. **46:** 1440 (Nov. 11) 1949.

The increased food requirement of children in a sea climate is discussed. An important factor is an increased appetite, partly due to the cooling, with its consequences.

AMBERG, Rochester, Minn.

PANCREATIC FUNCTION IN TOXICOSIS. PETER V. VÉGHELYI, Paediat. danub. **5**: 234 (March-April) 1949.

The output of pancreatic enzymes was studied in 19 infants, in the state of toxicosis. Pancreatic excretion was low in all of them. While this function almost ceases in generalized infections of all kinds and also during circulatory collapse, it is not inhibited by atrophy from inanition, dehydration, alkalosis, acidosis or circulatory disturbance by themselves.

Steatorrhoea induced by lack of lipase leads to further loss of water and minerals. In the absence of trypsin the breakdown of proteins is incomplete and thus amino acid deficiency arises. Pancreatic juice probably has some further important protective action on the liver. FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

CHRONIC POISONING DUE TO EXCESS OF VITAMIN A: DESCRIPTION OF THE CLINICAL AND ROENTGEN MANIFESTATIONS IN SEVEN INFANTS AND YOUNG CHILDREN. JOHN CAFFEY, Pediatrics **5**: 672 (April) 1950.

The clinical manifestations, the roentgenographic changes in the skeleton and the elevation of blood vitamin A are reported in a group of 7 infants and younger children poisoned by ingestion of excessive quantities of vitamin A and D concentrates over periods of several months.

The differential features of vitamin A poisoning and infantile cortical hyperostosis are discussed.

Three types of vitamin A and D concentrates commonly used in routine pediatric prophylaxis were found to be toxic when ingested in sufficiently large quantities over sufficiently long periods. The minimal preclinical latent period of vitamin A poisoning was about six months, and the minimal toxic daily dose was about 75,000 U. S. P. units.

Excessive dosage was due to overenthusiasm for vitamins and ignorance of the dangers of high vitamin intake.

The hazards of vitamin A poisoning from the routine prophylactic feeding of vitamin A and D concentrates to healthy infants and children on good diets are considerably greater than the hazards of vitamin A deficiency in healthy infants and children not fed vitamin concentrates.

CARDIAC AND AORTIC ARCH ANOMALIES IN THE OFFSPRING OF VITAMIN A DEFICIENT RATS CORRELATED WITH SIMILAR HUMAN ANOMALIES. JAMES G. WILSON and JOSEF WARKANY, Pediatrics **5**:708 (April) 1950.

The etiologic factors of congenital cardiac anomalies are discussed. It appears from clinical evidence that in some cases genetic factors and in others environmental factors may be responsible for the origin of cardiac malformations in children. It is of interest in this connection that cardiac and aortic arch anomalies were found in the offspring of female rats fed vitamin A–deficient diets prior to and during pregnancy. In the heart, failure of closure of the interventricular septum was observed. Among the aortic arch anomalies were right subclavian arteries arising distally from the descending aorta and coursing dorsal to the esophagus to reach the right shoulder; double (fourth) aortic arches, right aortic arches and many other variations from the normal pattern were observed. These cardiovascular anomalies were always associated with other congenital malformations, particularly of the eye and of the genitourinary tract.

INFLUENCE OF SHOCK DOSES OF VITAMIN B ON URINARY ELIMINATION OF NIACIN. G. NICHELE and F. GODANO, Arch. ital. pediat. e puericolt. **13**: 412, 1950.

Reduction of urinary excretion of nicotinic acid has been found by the authors after administration of large doses of vitamin B_1.

They surmise that a close relation exists between these two vitamins.

The authors admit the possibility that the nicotinic acid may be present in the urine in other forms as trigonelline and nictoninuric acid.

FROM THE AUTHORS' SUMMARY.

HOW THE INJECTION OF VITAMIN B_1 AFFECTS THE SMALL VESSELS OF THE SKIN AND THE TIME OF ABSORPTION OF EDEMA FLUID. P. NICOLAJ, Clin. pediat. **31**: 77 (Feb.) 1949.

Fifteen children were given injections of 15 to 50 mg. of vitamin B_1 daily for four days. No change in the appearance or pressure of the capillaries was observed, but several of the children showed an increase in capillary fragility and a more rapid absorption of induced edema fluid following the injections. HIGGINS, Boston.

ACTION OF THE PELLAGRA-PREVENTING VITAMINS–NICOTINE ACID AND NICOTINAMIDE ON THE BLOOD CAPILLARIES OF THE SKIN AND ON THE ABSORPTION OF INDUCED EDEMA. P. NICOLAJ, Clin. pediat. **31**: 150 (March) 1949.

In observations on children 6 to 12 years of age, nicotinamide and nicotinic acid were observed to have a double action on the skin capillaries. The early action, probably pharmacodynamic, involves dilation of the capillaries and increased capillary pressure and blood flow. The later action, probably vitaminogenic, involves the bringing of the fluid balance between the tissues and the capillaries to normal status.

HIGGINS, Boston.

EFFECT OF AN OILY VEHICLE FOR VITAMIN D ON THE BLOOD SERUM LIPASE. A. DE BLASIO, Pediatria **57**: 542 (July) 1949.

When vitamin D_2 (250,000 international units) or vitamin D_3 (600,000 international units) in olive oil was fed to children, an increase in blood lipase activity was detected. No such increase was found when plain olive oil or vitamin D_2 (600,000 units) in alcohol was fed.

HIGGINS, Boston.

VITAMIN E AND HEPATIC, CARDIAC AND MUSCULAR GLYCOGEN. PAOLO PROSPERI, Riv. di clin. pediat. **48**:1 (Jan.) 1950.

Prosperi studied the behavior of the muscular, cardiac and hepatic glycogen in guinea pigs treated with vitamin E.

The hepatic glycogen level fell in the first two hours after an intramuscular injection of vitamin E and increased after four hours; there was a parallel behavior of the muscular and myocardial glycogen. After five and ten days of treatment with vitamin E, the muscular, myocardial and hepatic glycogen had increased. In animals submitted to muscular activity and pretreated with vitamin E for twenty days, the cardiac, muscular and hepatic glycogen had increased in comparison with that of the animals submitted to muscular activity but not treated with vitamin E. The same results were obtained in guinea pigs submitted to a muscular activity not long after a single injection of vitamin E. In pregnant guinea pigs treated with vitamin E, the muscular, cardiac and hepatic glycogen had

increased in comparison with that of the nontreated pregnant ones. In the fetus of guinea pigs treated with vitamin E, the muscular and hepatic glycogen showed a marked increase.

The author advances the hypothesis that vitamin E exerts a real synthetic glycogenic action, especially in the myocardial and muscular tissues, and assumes that vitamin E takes part in the resynthesis of glycogen, acting perhaps in the transition period from the monophosphates to the diphosphates. A very high dose of vitamin E might strengthen the bonds between creatine, which is necessary for the transformation of glycogen into glucose.

The author, referring to the results obtained in the fetus of the pregnant guinea pig and after having pointed out the relation of vitamin E to the endocrine glands, especially with the gonads and the hypophysis, mentions the favorable possibility of using vitamin E in the treatment of premature infants.

FROM THE AUTHOR'S SUMMARY.

BLOOD LEVELS OF VITAMIN A IN ALCOHOL-SOLUBLE AND IN OILY PREPARATIONS BY MOUTH: DESCRIPTION OF METHOD OF EXTRACTION AND DOSAGE. ALVARO MASI, Riv. di clin. pediat. **48**:81 (Feb.) 1950.

The author reports the results he has obtained after a comparative treatment with very high doses of vitamin A administered orally, both in an oily and in an alcoholic solution.

He also reports the method of extracting vitamin A from organic material and of determining dosage with an electric spectrophotometer.

FROM THE AUTHOR'S SUMMARY.

BERIBERI HEART. R. MUÑOZ ENCISO and ARTURO GOMEZ LARA, Bol. med. d. hosp. inf. **6**: 63 (Feb.) 1949.

The authors present the case of a 10 year old girl who was suspected of having beriberi heart. The data from the laboratory and the roentgenology department strongly supported that diagnosis. Although slight symptoms produced by lack of thiamine are rather frequent, typical beriberi and beriberi heart are rare. The main points on which this diagnosis was established were these: 1. The heart was dilated without an apparent cause. There was no cardiac rheumatism, myocarditis, endocarditis or other cardiac abnormality. 2. The cardiac enlargement was mostly at the expense of the right cavities. 3. The electrocardiographic study suggested cardiac hypertrophy. 4. There was no response to digitalis. 5. The dilatation and cardiac insufficiency improved rapidly with large doses of thiamine. 6. There was edema, the presence of which may be explained by cardiac insufficiency and by the decrease of serum albumin.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL EXPERIENCES WITH BIOSIN IN BABIES. J. SVEJCAR and J. HOMOLKA, Ann. pædiat. **174**:175 (March) 1950.

1. The levels of biotin in the blood and urine were estimated by a biologic method in normal children. The average was 0.04 per cent in the blood and 1.5 per cent in the urine. In the milk of mothers feeding normal children 1.8 per cent was found. This amount, found normally in the milk of nursing mothers, is lower in Czechoslovakia than in other countries.

2. In entirely breast-fed children with Leiner's disease (erythroderma desquamativum) the corresponding levels were estimated. They were on the whole 56

per cent lower than in the normal children. In 7 cases in which the levels were controlled during the therapy with biotin a continuous rise took place during the treatment. As in cases previously observed, the biotin therapy was followed by quick improvement, sometimes with a complete cure of the disease.

3. In 5 children with *allaitement mixte* or artifically fed who had erythroderma desquamativum (Leiner) the levels of biotin in the blood were normal and in the urine high. Biotin therapy was also here successful, but more biotin and more time was needed. All these children had a general as well as the dermatologic disease.

4. The levels of biotin in the blood and urine in 11 cases of other kinds of dermatitis were determined by analysis. In those cases with low levels in the blood, the disease if it was of the seborrheic variety improved with the intake of cow's milk or during biotin therapy.

5. The authors conclude that erythroderma desquamativum (Leiner) in breast-fed children is caused by a lack of biotin in the milk of the nursing mothers and is sometimes aggravated by secondary infection. In artificially fed babies the lack of biotin is caused by general toxic infective influences which increase the requirement of the vitamin and inhibit the possibility of its use in the body tissues.

From the Authors' Summary.

Prematurity and Congenital Deformities

Leptomeningeal Changes Associated with Lipochondrodystrophy (Gargoylism). K. R. Mage, Arch. Neurol. & Psychiat. **63**:282 (Feb.) 1950.

Extensive involvement of the leptomeninges is described in a case of gargoylism. The changes were characterized by greatly thickened and dense membranes, with resultant compression of the cortex.

McGuigan, Evanston, Ill.

Congenital Malformations with Severe Damage to the Central Nervous System Due to Early Fetal Virus Infection. Lotte Lande, J. Pediat. **36**:625 (May) 1950.

Lande studied a group of 16 children in institutions who had malformations resembling the postrubella syndrome. A history of maternal rubella was obtained for 7 children. A severe common cold within the first three months of pregnancy had occurred in 5 mothers. One mother had had virus influenza. Apparently 5 to 6 per cent of the congenital malformations of heretofore unknown etiology in children in institutions may be attributed to early fetal virus infection.

Macdonald, Pittsburgh.

The Adequate Care of the Premature Infant. Peter H. Spohn, Canad. M. A. J. **62**:317 (April) 1950.

Mortality rates in two large Vancouver (British Columbia, Canada) hospitals over twelve years showed no appreciable improvement. The author feels that standards such as those of the American Academy of Pediatrics should be adopted to provide a uniform definition of prematurity. Improvement could be attained by complete records on premature infants, autopsies in all fatal cases, regular conferences between pediatric, obstetric and pathology departments and careful attention during the first forty-eight hours.

McGuigan, Evanston, Ill.

ASYMMETRIC ECTRODACTYLY, SYNDACTYLY AND BRACHYMESOPHALANGY. D. P. R. KEIZER, Maandschr. v. kindergeneesk. **17**:388, 1950.

A 6 year old boy showed ectrodactyly of the third finger of the right hand with syndactyly of thumb and index fingers, brachymesophalangy of the second, fourth and fifth fingers, pilonidal sinus, spina bifida, a short right leg with four toes and four metatarsal and two cuneiform bones. No hereditary and no exogenous influences were found.

FROM THE AUTHOR'S SUMMARY.

EMBRYOPATHOLOGY. M. LAMY, Wien. klin. Wchnschr. **62**:237 (April 14) 1950.

The lecture emphasizes the necessity of differentiating hereditary malformations from those malformations which are due to erogenous causes. The hereditary abnormalities are gene conditioned, genotypic, and may become manifest later in life. The other abnormalities or diseases may be due to injuries acting on the developing fetus. Such injuries as are produced by roentgen rays in man, or by a disease of the mother, like German measles, act during the first three months of life. It is to be noted that during this period changes in genes and changes in internal factors may have the same effect on the differentiation of the organs and tissues. Later in pregnancy other lesions may be produced, giving rise to other congenital diseases. The difficulties of establishing numerical relationship in dominant or recessive types of hereditary abnormalities are discussed.

AMBERG, Rochester, Minn.

PARTIAL ALBINISM WITH DEAF-MUTISM, BLEPHAROPHIMOSIS AND MYO-OSTEO-ARTICULAR DYSPLASIA. D. KLEIN, Helvet. pædiat. acta **5**:38 (March) 1950.

A peculiar dysmorphia composed of ectodermal and mesodermal elements in a 10 year old girl is described. The salient features were (1) partial albinism with blue eyes and deaf-mutism; (2) deformity of the skull (absence of the naso-frontal angle, widening of the root of the nose, high arched palate, defective implantation of the teeth and hypoplasia of the ascending rami of the mandible with retrognathism); (3) antimongoloid obliquity of the lid fissures; widening of the distance of the internal and external angles of the eyes with blepharophimosis ("ankyloblepharon") and dystopia of the inferior lacrimal points (van der Hoeve–Halbertsma–Waardenburg syndrome); (4) amyoplasia and multiple rigidity of the joints of the upper limbs (Rocher-Sheldon syndrome); (5) dysplasia of the skeletal system (aplasia of the first rib on the left, hypoplasia of the first two ribs on the right, pronounced angulation of the thorax in the lateroposterior segment, rudimentary differentiation of the carpal bones, formation of cysts in the para-articular region of the elbows and in the sacrum, generalized osteoporosis); (6) webbing of both axillary folds and of the fingers of both hands.

The symptomatology of this dysmorphia is analyzed and its relation to other conditions having some common symptoms with it are discussed. In addition, the points of analogy with some malformations of the comparative biology are shown.

The genotypic origin of the clinical entity seems to be composed of features known as hereditary.

In view of the complexity of the syndrome composed of several hereditary elements of ectodermal and mesodermal origin, one is led to assume a mutation, probably in connection with a chromosome aberration.

The different symptoms encountered in this dysmorphia are interpreted as being the consequence of an inhibitory effect of the altered genic complex on the different morphogenetic processes in the very early embryogenetic period (critical phase between the sixth and eighth weeks).

From the Author's Summary.

Newborn

Megacolon in the Newborn. Editorial, Am. J. Digest. Dis. **15**:134 (April) 1948.

Intestinal obstruction in a 3 day old infant is described. One hundred and fifty normal newborn infants were observed to have multiple redundancies in the colon with a striking variation in size. If the pathogenesis of Hirschsprung's disease (congenital megacolon) is dysfunction of evacuation, is constipation in the adult an abortive megacolon?

Kimball, Evanston, Ill.

An Anti-Rh Antigen-Antibody Reaction Factor (the Rh-Protective Factor): Preliminary Report. Allan Bloxsom and Rose Matthael, Bull. Johns Hopkins Hosp. **82**:1 (Jan.) 1948.

On the theory that Rh-negative blood might possess some factor that inhibits the Rh-antigen-antibody reaction, the authors tested the effects of Rh-negative and Rh-positive serums on the agglutination of Rh-positive cells with Rh-negative diagnostic serums and with serums containing anti-Rh agglutinins. The authors claim to have demonstrated a factor in the serum of Rh-negative persons which inhibits the agglutination of Rh-positive cells by anti-Rh agglutinins. The number of persons tested is not large and the differences are not striking.

Lyttle, Los Angeles.

Role of Transfusion in the Etiology of Erythroblastosis: A Warning to Physicians. L. M. Hellman and G. R. Vosburgh, J. A. M. A. **136**:79 (Jan. 10) 1948.

The case histories of 9 Rh-negative women who received transfusions are presented. Before transfusion these 9 women had delivered 5 healthy babies and 2 dead ones. After transfusions, they delivered 2 normal infants and 8 erythroblastotic infants, 4 of whom died. The fathers of the 2 normal babies and 1 of the erythroblastotic infants who lived were heterozygous. The fathers of the other 6 infants were homozygous and the prognosis for future normal children was 0. The authors are of the opinion that the administration of Rh-positive blood serves as a more powerful immunizing agent than the repeated bearing of Rh-positive children. All women who will bear children should receive Rh-compatible blood or Rh-negative blood.

Kimball, Evanston, Ill.

Newborn Mortality and Morbidity with Continuous Caudal Analgesia: An Analysis of Cases in New York, Philadelphia and Memphis, with Controls. Robert A. Hingson, Waldo B. Edwards, Clifford B. Lull, Frank E. Whitacre and H. Charles Franklin, J. A. M. A. **136**:221 (Jan. 24) 1948.

The studies involved the analyses of 7,893 births that took place in three institutions: the Philadelphia Lying-In Unit of the Pennsylvania Hospital, the

United States Marine Hospital, New York, and the John Gaston Hospital, Memphis, Tenn. Five thousand and fifty-nine mothers were delivered while under continuous caudal analgesia and 2,834 while under analgesia induced by some other method but none were under anesthesia. The number of still births and neonatal mortalities was significantly improved in the groups given caudal analgesia; mortality rates were also better among the premature infants. The infants breathed more quickly and fewer resuscitations were necessary in all groups in which caudal analgesia was used.

KIMBALL, Evanston, Ill.

A HOSPITAL ROOMING-IN UNIT FOR FOUR NEWBORN INFANTS AND THEIR MOTHERS. EDITH B. JACKSON, RICHARD W. OLMSTED, ALAN FOORD, HERBERT THOMS and KATE HYDER, Pediatrics **1**:28 (Jan.) 1948.

The plan and procedures for setting up a four bed, semiprivate, rooming-in unit as established in October 1946 at the Grace-New Haven Community Hospital, New Haven, Conn., are discussed. The rooming-in unit was organized through the cooperative interest of the departments of pediatrics and obstetrics of the Yale University School of Medicine, the Yale School of Nursing and the hospital administration. Rooming-in is the term adopted to designate the hospital arrangement whereby a mother may have her newborn baby in a crib by her bedside whenever she wishes. The advantages of keeping mother and newborn infant close together are considered from the point of view of both the mother's and the infant's welfare. Mothers are selected for the unit in the prenatal clinic on the basis of wanting to nurse and wanting rooming-in. There is a nurse in attendance in the unit around the clock for the care of both mothers and infants. The over-all results of a time study of nursing care undertaken by members of the rooming-in staff is recorded. The babies are on a so-called *ad libitum* or self-demand schedule. The mothers learn to take care of their babies before they leave the hospital on the eighth day. Only two visitors in addition to the father are permitted. The father is allowed, even encouraged, to hold the baby during visiting hours. The reactions of the mother have been uniformly favorable. The value of the rooming-in unit as an educational experience for pediatricians in training, for student nurses and for parents is indicated. FROM THE AUTHORS' ABSTRACT.

ANAEROBIC METABOLISM IN THE NEWBORN INFANT: I. ON THE RESISTANCE OF THE FETUS AND NEWBORN TO OXYGEN LACK. JAMES L. WILSON, HELEN S. REARDON and MAKIO MURAYAMA, Pediatrics **1**:581 (May) 1948.

A short review is given of various research efforts which led to the conclusion that the human fetus and newborn infant, as well as the newborn of lower animals, have a partially anaerobic type of metabolism which they lose soon after birth. This seems to be of a nature which allows metabolism to be carried on with less than the usual consumption of oxygen and less than the usual production of carbon dioxide. It possibly makes use of an end point of carbohydrate breakdown short of carbon dioxide. A report is given on observations by other workers on animals, on observations by other workers and the authors on acid-base studies in the human infant and on observations by the authors of the response in the respiratory ryhthm of premature babies to the administration of oxygen-enriched atmospheres. It is pointed out that a fairly consistent change from an anoxic type of irregular respiration to a regular type occurs on administration of oxygen, a change which suggests that there was a previous defect in oxygen absorption. They point out that this defect exists in spite of the fact that many studies indicate a carbon dioxide level in plasma distinctly below that observed in old animals,

adults and children and a true acidosis as measured by the p_H value of the blood. All this is of theoretic interest as it bears on fetal physiology and of a certain practical importance. The study indicates (1) the possible benefit from oxygen therapy even in healthy premature infants, (2) the fact that a low carbon dioxide level and a true acidosis are normal and usual in premature babies and except when excessive need not be combated by attempts to give alkalines by mouth and (3) the possibility that results of previous studies of basal metabolism in premature infants may be inaccurate because of failure to estimate the anaerobic part of the metabolism.

FROM THE AUTHORS' SUMMARY.

FORMULA ROOMS FOR NEWBORN INFANTS IN LYING-IN HOSPITALS: A PRELIMINARY STUDY ON SUPERVISION AND CERTAIN TECHNICS FOR PREPARATION. HELEN M. WALLACE, HAROLD ABRAMSON and MARGARET A. LOSTY, Pediatrics **1**:758 (June) 1948.

The formula rooms and certain procedures of 113 hospitals having maternity services and services for the newborn in New York city were studied by members of the New York City Department of Health. Observations showed lack of supervision of formula preparation, the use of untrained personnel and the limited use of some type of terminal sterilization of formulas. These inadequacies were more evident in hospitals with smaller maternity services and nurseries for the newborn.

A review of the literature revealed few references to methods of terminal sterilization of formulas. Considerable variation in opinion prevailed concerning the temperature required and the time of application necessary to assure safe feedings. Furthermore, opinions differed with regard to the pressure versus the nonpressure methods of steam sterilization. Little or no bacteriologic evidence supported opinions that were advanced. A survey by the questionnaire method of 33 pediatricians, public health worker, executives of 3 commercial milk companies and 2 nutritionists showed essentially the same variation.

The need for further controlled studies in this field is emphasized.

FROM THE AUTHORS' SUMMARY.

DERMATITIS EXFOLIATIVA OF THE NEWBORN (RITTER'S DISEASE). E. REZZA, Lattante **19**:100 (Feb.) 1948.

Two cases of dermatitis exfoliativa in newborn children are reported. The origin is believed to be pyogenic and secondary to pemphigus. One of the infants recovered after treatment with penicillin and sulfathiazole.

HIGGINS, Boston.

CLINICAL DIPHTHERIA IN THE NEWBORN INFANT. E. SARTORI and M. BOLLETTI, Lattante **19**:285 (May) 1948.

In the years 1944 to 1946, 10 small infants with diphtheria were seen in the pediatric clinic of the University of Pavia, Italy. Five of these 10 were newborn infants, being 9, 10, 10, 10 and 19 days old; 3 of the newborn infants died of the disease. The general conception that infants as young as these are not susceptible to diphtheria appears to be subject to modifications.

HIGGINS, Boston.

ICTERUS GRAVIS OF THE NEWBORN WITH ERYTHROBLASTOSIS. G. SANSONE and MARGHERITA BERTOLLI, Pediat. med. prat. **23**:63 (March) 1948.

A fatal case of erythroblastosis with jaundice in a newborn baby is reported. The mother had clinical symptoms of nausea, vomiting, asthenia, dizziness, constipation and insomnia and an "earthy" complexion during the pregnancy. The father was of blood group A Rh positive and the mother of group B Rh negative. The mother's serum showed a prozone reaction in the agglutination tests.

HIGGINS, Boston.

CLINICAL ANATOMICOPATHOLOGIC STUDY OF A NEWBORN INFANT WITH SEVERE FAMILIAL ICTERUS WITH ERYTHROBLASTOSIS DUE TO RH INCOMPATIBILITY. GENNARO SANSONE, Policlinico inf. (supp.) **16**:30 (Jan.) 1948.

The case of a newborn infant who died at 4 days of age with signs of a severe jaundice with erythroblastosis is described. Two previously born siblings were alive. The first was well, and the second, who was jaundiced in the early days of life, had recovered with typical neurologic sequelae. The pathologic examination confirmed the clinical diagnosis. The brain, which showed severe nuclear jaundice, had the most striking lesions. Histologically, the changes, most pronounced in the basal ganglions, were also widespread in the cortex. The Rh grouping and the detection of antibodies in the maternal serum showed the cause of the disease.

FROM THE AUTHOR'S SUMMARY.

TETANUS NEONATORUM. I. VAN DER HAL, Maandschr. v. kindergeneesk. **16**:119 (April) 1948.

Before the last war tetanus neonatorum in the Netherlands was rare; since then the number of cases has increased considerably. No indication was found that this increase was due to poorer hygienic measures. It is possible that the infection occurs by means of fecal contact during delivery, as the feces often contain tetanus bacilli. The prognosis has greatly ameliorated during the last few years. This is partly due to the administration of concentrated and highly purified antitoxin and penicillin. Improved measures in nursing also had a favorable influence. The antitoxin must be given in a sufficient amount on the first day, or on the first and second days, of the illness by the intravenous and intramuscular routes.

In the Children's Hospital of the University of Groningen, Netherlands, 100,000 to 200,000 antitoxic units was injected. In many clinics penicillin is not used because its efficiency in inhibiting the growth of Clostridium tetani is doubted. Herrell demonstrated that tetanus bacilli were sensitive to penicillin in vitro. The favorable effect of penicillin can be explained partly by its removal of secondary infection, through which the tetanus bacilli are indirectly inhibited. Penicillin, $8 \times 6{,}000$ units, was injected intramuscularly; also, penicillin was applied locally in an ointment containing 1,000 units per gram.

The following general measures have to be taken: Administration of stimulants must be avoided to minimize the number of convulsive attacks. The patient must be nursed in a dark, silent room. Examination of blood and spinal fluid is omitted. The diapers are changed as infrequently as possible. Feeding by gavage is nearly always necessary. The gavage tube can be left in situ. Chloral hydrate is given as a sedative. Subcutaneous injection of a 25 per cent solution of magnesium sulfate or rectal administration of tribromoethanol (avertin®) may be used.

VAN CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

THE EFFECTIVENESS OF PENICILLIN IN THE TREATMENT OF NASOPHARYNGEAL DIPHTHERIA. EDWARD W. BIXBY, Am. J. M. Sc. **215**:509 (May) 1948.

In a series of 139 patients with diphtheria, treatment with penicillin was followed by a decrease in the incidence of carriers, if the drug was given early in the course of the disease. There was also a shorter period of hospitalization for those treated early with penicillin than for the others. The incidence of postdiphtheritic complications was not affected by the use of penicillin; however, the severity of complications was modified. A suggestion is made as to the possible mode of action of penicillin.

HENSKE, Omaha, Neb.

A FAMILIAL SPREAD OF VACCINIA WITH ONE DEATH: ISOLATION AND IDENTIFICATION OF THE VIRUS. FRIEDA G. GRAY, Bull. Johns Hopkins Hosp. **82**:538 (May) 1948.

Three cases of generalized vaccinia developed by direct contact from a 6 month old vaccinated infant. The incubation period was thirteen days in a 3 year old brother, sixteen days in the 41 year old mother and 4 year old brother.

The 3 year old patient was known to have eczema but had been on a restricted diet and free of lesions for about one year. He became severely ill with the vaccinia, having widespread lesions, and died thirty-six hours after his admission to the hospital. The appearance of histologic sections of the skin was characteristic of vaccinia and showed many intracytoplasmic inclusion bodies. A filtrable agent capable of producing vaccinia-like lesions in rabbits was isolated from this child and carried through sixteen successive rabbit passages. The virus was identified as vaccinia by neutralization tests employing known vaccinia immune serum.

LYTTLE, Los Angeles.

THE CLINICAL MANIFESTATIONS OF THE SEVERE FORM OF DIPHTHERIA. A. MURRAY FISHER and SIDNEY COBB, Bull. Johns Hopkins Hosp. **83**:297 (Oct.) 1948.

The authors note that there have been a rise in the incidence of diphtheria in the last few years, an increase in the severity and a tendency to a rising age incidence. The article is a complete analysis of the clinical and laboratory features of severe cases of diphtheria in 30 patients. The authors stress the fact that there was a high incidence of myocardial involvement; 12 of the 30 patients in their series had a previous history of immunization against diphtheria; 6 of the 30 strains of diphtheria bacilli isolated were reported as avirulent, which throws some doubt on the accuracy of the virulence test, and the average duration of the acute infection from onset to the time antitoxin was given was 4.7 days. This delay in treatment was probably the most important cause of serious complications or death.

LYTTLE, Los Angeles.

MENINGOCOCCIC INFECTIONS. WALTER M. WHITAKER, Illinois M. J. **93**:24 (Jan.) 1948.

A study was made of 116 patients with meningococcic infections. These infections are primarily septicemic. The mortality rate seems to parallel the intensity and severity of the cutaneous lesions. A mortality rate of 1.72 per cent in the patients treated is indicative of the tremendous advance in therapy in this disease. There is no evidence to substantiate the value of routine employment of antitoxin

in the treatment of these patients. Early diagnosis with prompt institution of chemotherapy and maintenance of a high concentration of the drug in the blood and spinal fluid lead to control of the infection and ultimate recovery in 98 per cent of meningococcic infections.

BARBOUR, Peoria, Ill.

IMMUNIZATION PROCEDURES. JEROME J. SIEVERS, Illinois M. J. **93**:153 (March) 1948.

Sievers outlines the present status of those immunization procedures which are effective against diseases currently present in Illinois. With the waning of previously acquired immunity, and consequently with the absence of immunity in newborn infants, the schedules of immunization which were formerly employed will have to be reconsidered. The growing evidence of the efficacy of combined antigens is resulting in a decrease in the number of injections required in a full immunization schedule.

Primary vaccination against smallpox should be done in the first year of life. Frequent revaccinations are necessary to maintain immunity. The decline in morbidity and mortality due to diphtheria has resulted in a decrease in the frequency of naturally acquired stimuli to immunity and a consequent decrease in the general level of immunity in certain sections of the population. The last few years have seen a definite shift of the incidence of the disease into persons of the older age groups. It is no longer possible to assume that infants are immune to diphtheria during the early months of life. Also as a result of the reduced prevalence of diphtheria bacilli, artificially induced immunity is not as lasting as it once was.

The desirability of beginning primary immunization to diphtheria at an earlier age, the more frequent use of stimulating injections of the antigen and the extension of immunization to persons of the older age groups must be considered. Diphtheria immunization may be satisfactorily combined with administration of pertussis vaccine, tetanus toxoid or both. A stimulating or booster dose is indicated at the time of entrance to school or earlier. With the presently available antigens and their severe reactions, physicians are not yet ready to advise the mass immunization of adults.

Immunization measures against whooping cough may be started as early as 1 month of age and should not be delayed beyond the seventh month. The vaccine may be given alone or in combination with diphtheria toxoid, tetanus toxoid or both. A stimulating dose of pertussis vaccine is indicated at the time of entrance to school or earlier.

It is added protection to include tetanus toxoid with diphtheria toxoid when the latter is given during the first year, or to administer it singly during the second or third year. A booster dose is suggested one or two years after the original immunization and at the time of any injury subject to contamination with tetanus spores. It is also strongly recommended that active immunization with tetanus toxoid be started about three weeks after any administration of tetanus antitoxin.

The use of injections of scarlet fever streptococcus toxin as a mass immunization procedure in the general population is not recommended. Typhoid immunization is indicated where, because of occupation or local sanitary conditions, the risk of exposure is great.

The use of influenza virus vaccine, types A and B, seems to provide a significant degree of protection against the clinical types of influenza for which these organisms are responsible. The disease as currently seen is relatively mild, and the desirability of widespread immunization is still unsettled.

The wide distribution of Rocky Mountain spotted fever throughout the state indicates that the common wood ticks of Illinois are infected with the Dermacentroxenus rickettsi (Rickettsia rickettsi). It may be well, therefore, for all persons who, because of residence or occupation, are exposed to the bite of ticks to consider the use of Rocky Mountain spotted fever vaccine.

BARBOUR, Peoria, Ill.

IMMUNIZATION OF CHILDREN WITH INFLUENZA VIRUS VACCINE. R. E. DUKES and JAMES B. GILLESPIE, Illinois M. J. **93**:252 (May) 1948.

A report is given of a study of immunizations against influenza carried out by the authors during October, November and December 1946. A group of 100 children was immunized with influenza virus vaccine, types A and B, N. N. R.; a group of similar size served as controls and was not immunized with the vaccine. Immunization consisted of two injections of the vaccine, 0.5 cc. in each injection, at an interval of one week. In 14 children, smaller doses were given rather than the adult doses. Reactions subsequent to the first injection of influenza virus vaccine were frequent. Only 12 patients had reactions following the second injection, and in all instances these were mild. The incidence of influenza in the immunized and control groups was not unlike except for the children of the youngest age group, in which the incidence of influenza was much less frequent in the immunized children. The effectiveness of immunization was not impressive in this series.

BARBOUR, Peoria, Ill.

PERTUSSIS IMMUNIZATION. JOSEPH A. BELL, J. A. M. A. **137**:1276 (Aug. 7) 1948.

Two doses of an alum-precipitated mixture of pertussis vaccine and diphtheria toxoid which contained only 10,000,000,000 killed Hemophilus pertussis organisms per dose were given at four week intervals to children in a general population from 2 to 23 months of age and whose birth date was in an odd month. Two doses of diphtheria toxoid were given to similar children whose birth date was in an even month. The attack rate of whooping cough averaged 11.1 per cent in the treated group, as compared with 41.0 per cent in the control group. The duration and severity of the cough were less in the treated groups and the criteria used for diagnosis the same in each group, but they were not as conservative as those used in other reported series.

KIMBALL, Evanston, Ill.

PRIMARY PNEUMONIC PLAGUE IN MUKDEN, 1946, AND REPORT OF 39 CASES WITH THREE RECOVERIES. T. H. TIEH, E. LANDAUER, F. MIYAGAWA, G. KOBAYASHI and G. OKAYASU, J. Infect. Dis. **82**:52 (Jan.-Feb.) 1948.

An outbreak in Mukden, China, of primary pneumonic plague with 39 cases, 28 of which were confirmed, is reported. The disease was probably introduced by an incubationary carrier who came from an epidemic region. Control measures against primary pneumonic plague apparently checked the outbreak.

Treatment with sulfadiazine was effective in 3 of 5 patients. The 2 treated patients who died apparently did not receive the drug early enough. Four of 42 healthy persons examined were found to harbor virulent Pasteurella pestis in the throat for six to fifteen days after their last exposure to patients with the primary pneumonic plague. In the authors' opinion, at least 1 of the 4 was a true healthy carrier.

FROM THE AUTHORS' SUMMARY.

LABORATORY STUDY OF THE EPIDEMIOLOGY OF POLIOMYELITIS. F. B. GORDON, F. M. SCHABEL JR., A. E. CASEY and W. I. FISHBEIN, J. Infect. Dis. **82**:294 (May-June) 1948.

Methods and results are described of tests for detection of poliomyelitis virus in the stools collected during an epidemiologic study in Chicago in 1945. Pools of daily stool collections from 76 persons were tested by inoculation of 2 monkeys each. Of 23 household contacts, 17 (74 per cent) were infected as evidenced by virus in the stool. The incidence of infection in extrahousehold contacts was 9 (39 per cent) of 23 and in noncontacts living in the same neighborhood 2 (11 per cent) of 18. None of 5 persons from nonpoliomyelitis (control) neighborhoods and 1 of 7 unclassified persons was infected.

These results are interpreted as indicating that during this epidemic period contact with an infected person was the usual source of infection within the groups studied rather than any general widespread factor in the neighborhood.

FROM THE AUTHORS' SUMMARY.

ERYTHROCYTE SEDIMENTATION RATE DETERMINATIONS IN POLIOMYELITIS AND OTHER INFECTIONS OF THE CENTRAL NERVOUS SYSTEM AND MENINGES. T. L. HARTMAN and L. WEINSTEIN, J. Pediat. **33**:462 (Oct.) 1948.

Studies of the erythrocyte sedimentation rate in 65 patients with poliomyelitis and in 46 patients who had abnormalities of the spinal fluid were performed. Although the sedimentation rate as determined by a modified Westergren technic was elevated in approximately 50 per cent of those with early poliomyelitis, the authors concluded that the test was not helpful in differentiating the disease from other infections of the central nervous systems, whether bacterial or viral in origin. Furthermore, they observed no correlation between the erythrocyte sedimentation rate and clinical type, severity or degree of abnormality of the cerebrospinal fluid.

GRULEE JR., Galveston, Texas.

MENINGOCOCCAL PNEUMONIA: REPORT OF TWO CASES WITH MENINGOCOCCAL EFFUSION IN ONE. IRVING B. BRICK, New England J. Med. **238**:289 (Feb. 26) 1948.

The 2 cases reported were of male adults in the fifties. One case was of meningococcic pneumonia with meningococcic pleural effusion; the literature was reviewed.

In epidemics of meningococcic infection with or without meningeal involvement, careful bacteriologic studies will probably uncover more cases of meningococcic pulmonary involvement than are reported at present. GENGENBACH, Denver.

DIPHTHERITIC MYOCARDITIS. NORMAN H. BOYER and LOUIS WEINSTEIN, New England J. Med. **239**:913 (Dec. 9) 1948.

The effect of diphtheria toxin on the myocardium of 93 patients with clinical diphtheria was assessed by the authors by means of at least five electrocardiograms taken during the course of the illness. Sixty-one abnormal tracings were secured, and the criteria for grading them in respect to severity are given. In general, most of the electrocardiographic changes occurred in the children of the older age groups, although age was not a factor in determining the degree of change. The number of deaths rose as the grade of abnormality increased, the major pathologic observations being muscle degeneration, diffuse fibrosis and loss of muscle fibers. The lack of correlation between clinical findings and electrocardiographic changes is emphasized.

In the opinion of the authors, nonfatal diphtheritic myocarditis may leave the heart permanently damaged, though competent, and this damage may be evidenced by decreased cardiac reserve in the face of the degenerative myocardial diseases of later life.

Arguments for the mobilization of the patient with electrocardiographic changes before these changes have reverted entirely to normal are given.

WHEELOCK, Denver.

RECENT CONCEPTS REGARDING THE SPREAD AND TREATMENT OF POLIOMYELITIS. ROBERT B. LAWSON, New England J. Med. **239**:994 (Dec. 23) 1948.

Poliomyelitis virus has a worldwide distribution; clinically recognized epidemics of poliomyelitis infections are of relatively recent origin and have been particularly prominent in the countries with high standards of sanitation (this may mean that in countries with poorer sanitation infections occur in persons of the younger age groups with resulting immunity but are not associated with the usual signs of poliomyelitis). Close personal contact between apparently healthy carriers or persons with clinical cases and susceptible hosts plays an important role in this widespread dissemination of the virus. Something happens during the summer in the temperate zones to increase the dissemination of virus (this may be explained by insect transmission, but other possibilities, such as changes in the host or the virus itself, may prove to be more important).

Prevention of the spread of the virus implies restriction of the intimate contacts between children, fly-abatement programs and persistence of public health provisions known to achieve this end. Flare-ups of the clinical disease in carriers may be minimized by instruction aimed at preventing overexposure, chilling and performance of operations in regions of the upper respiratory tract. Attempts at safe immunization have so far been unsuccessful.

The author reviews the present concepts of treatment and discusses the use of antibiotic substances, tracheotomy, stimulants to the paretic bladder and the application of the useful portions of the Kenny technic. The use of curare and neostigmine preparations for relief of muscle spasm is discouraged.

WHEELOCK, Denver.

CLINICAL USE OF ALCOHOL-REFINED TOXOIDS. J. M. RUEGSEGGER and G. K. LOOSER, Pediatrics **2**:35 (July) 1948.

Toxoids of diphtheria and tetanus were refined by precipitation with methanol under rigidly controlled conditions of ionic strength, p_H, temperature and protein concentration. This method of refinement resulted in the elimination of 99.7 per cent of the nitrogen of the original culture filtrates. The combined toxoids of diphtheria and tetanus were inoculated into 31 adults and 550 children. Such inoculations were followed by many fewer and less severe reactions than those following the use of ordinary toxoids. The immunity thus conferred seems adequate and durable as adjudged by serial antitoxin titrations over the course of one year.

FROM THE AUTHORS' SUMMARY.

ISOLATION OF MUMPS VIRUS FROM THE BLOOD OF A PATIENT. LAWRENCE KILHAM, Proc. Soc. Exper. Biol. & Med. **69**:99 (Oct.) 1948.

Blood was obtained from a boy almost 4 years of age the first day of an attack of epidemic parotitis. The plasma and red cells separately, after two weeks' storage in solid carbon dioxide, were inoculated intra-amniotically on chick eggs.

Virus was detected in 4 of 8 amniotic fluids and in almost all the eggs on two subsequent passages. Inhibition of hemoagglutination and results of complement fixation tests confirmed the clinical diagnosis and identified the agent as the mumps virus.

HANSEN, Galveston, Texas.

Acute Infectious Diseases

ORAL PENICILLIN IN THE PROPHYLAXIS OF RECURRENT RHEUMATIC FEVER. M. M. MALINER and S. D. AMSTERDAM, J. Pediat. **31**:658 (Dec.) 1947.

The authors report on the use of penicillin troches containing 1,000 and 5,000 Oxford units dissolved slowly in the mouth, one after each meal, in the prevention of streptococcic infections in 22 patients with rheumatic fever. A similar group was used as controls. None of the children receiving penicillin prophylaxis showed signs of rheumatic activity during the two years of study. Recurrences occurred in 4 of the controls. The absence of toxic manifestations and the avoidance of blood studies and urinalyses with penicillin prophylaxis are pointed out. The authors conclude that further studies are warranted.

GRULEE JR., Galveston, Texas.

A FEW INTERESTING CASES OF MALIGNANT MALARIA. SALIL GHOSH, Indian J. Pediat. **15**:17 (Jan.) 1948.

Four briefly detailed case reports are presented. McGUIGAN, Evanston, Ill.

TYPHOID IMMUNIZATION IN INFANTS AND YOUNG CHILDREN. ABD EL AZIM EL GHOLMY and ALY OMAR, J. Roy. Egyptian M. A. **31**:405 (May) 1948.

A careful study of the result of typhoid immunization in infants and children up to the age of 5 years was carried out. One hundred and twenty children, aged 1 week to 5 years, were given the usual three doses at weekly intervals. It was observed that the resulting antibody titers were low and of short duration. The authors conclude that the vaccination of children under 5 years of age is of doubtful value.

McGUIGAN, Evanston, Ill.

SCHISTOSOMIASIS: THE EFFECT OF THE DISEASE ON EDUCATIONAL ATTAINMENT. F. G. LOVERIDGE and W. F. ROSS, South African M. J. **22**:260 (April 10) 1948.

Studies on white and native school children infected with schistosomiasis demonstrated a definitely adverse effect on the educational progress of the white children. The natives did not seem to be affected. McGUIGAN, Evanston, Ill.

SALMONELLOSIS (SALMONELLA SCHOTTMÜLLERI) AND BRUCELLOSIS TREATED WITH STREPTOMYCIN. GIULIO MURANO, Pediatria **56**:96 (Jan.-March) 1948.

After briefly reviewing the literature concerning the use of streptomycin in persons with typhoid, paratyphoid and brucellosis infections with doubtful and inconstant results, the author reports on 2 patients with paratyphoid and 1 with brucellosis that he personally observed. These were cured effectively with relatively moderate doses of streptomycin after an unsuccessful application of vaccines. On the strength of those 3 cases, he emphasizes that successful results may be ascribed to the combination of the newly introduced antibiotic with vaccine

therapy. Such a combination could, perhaps, favorably influence the course of the infection through various complex factors interfering with the in vivo activity of streptomycin, an antibiotic which is active, toward the organisms causing these diseases in vitro and experimentally.

FROM THE AUTHOR'S SUMMARY.

VARIATIONS IN THE SO-CALLED ELECTROLYTES OF PLASMA PROTEINS IN TYPHOID WITH REFERENCE TO VACCINE SHOCK. FILIPPO MULÈ, Pediatria **56**:45 (Jan.-March) 1948.

The variations in the electrolytic threshhold in the plasma of patients with typhoid was studied in regard to vaccine reaction. The data obtained are discussed.

FROM THE AUTHOR'S SUMMARY.

SALMONELLA INFECTIONS IN INFANTS. MÜNIRE YÜCEOĞLU, Ann. paediat. **171**:82 (Aug.) 1948.

A baby 5 months of age was admitted to the hospital on account of dystrophy due to excessive feeding of starch. A blood culture made on account of the presence of a splenic tumor and because malarial parasites could not be found in the blood showed a growth of Salmonella enteritidis (Bacillus Gärtner). A culture from mucus obtained by gastric lavage again produced S. enteritidis. A blood culture made on the tenth day of the illness had the same result. The last blood culture on the sixteenth day remained sterile.

This infant, therefore, was considered to have had a S. enteritidis septicemia which had a mild course with a moderate elevation in temperature, splenic tumor and bronchopneumonia, but without diarrhea. A few loose stools occurred during convalescence, but no S. enteritidis could be found in the stool cultures. The bacilli were seen in the blood even during the subfebrile course of the illness. Whether the bronchopneumonia was caused by the S. enteritidis, a possibility which has to be considered on account of the frequency of bronchitis in Salmonella infections, or whether the positive culture from the mucus obtained by gastric lavage was due to an infection of the alimentary tract, cannot be decided, but the negative findings in the stools make the latter assumption improbable.

FROM THE AUTHOR'S SUMMARY.

TOXOPLASMOSIS COMBINED WITH SITUS INVERSUS TOTALIS. S. VAN CREVELD, P. ARONS and J. I. DE BRUYNE, Ann. paediat. **171**:177 (Sept.) 1948.

A case of congenital toxoplasmosis in a girl with complete situs inversus is reported. The diagnosis of congenital toxoplasmosis was based on the presence of characteristic clinical symptoms and on the results of serologic tests. These tests included, for example, a new in vitro test recently elaborated by Sabin. A sister of this girl, born fifteen months after our patient, is now 9 months old and up to the present shows neither the clinical symptoms nor the serologic reactions of toxoplasmosis.

FROM THE AUTHORS' SUMMARY.

USE OF GAMMA GLOBULIN IN ABACTERIAL INFECTIONS. S. VAN CREVELD, Nederl. tijdschr. v. geneesk. **92**:1845 (June 19) 1948.

Gamma globulin contains nearly all the antibodies that can be demonstrated in the blood. Since gamma globulin is available, it is possible to administer antibodies in a far higher concentration than when serum or plasma is used. Administration

of gamma globulin has proved to be effective in preventing measles or in changing its course. Treatment with gamma globulin is recommended for prevention of homologous serum hepatitis.

When using gamma globulin in the treatment of virus infections, one must consider that the course of the disease may not be influenced. Gamma globulin does not penetrate the cells and, therefore, does not reach the virus already in the cells when the illness becomes manifest. The result of experimental investigations is in accordance with this theory. On the other hand, the administration of gamma globulin seems to be justified, as it is not known how far the invasion of the cells by the virus may have progressed.

Topping reported a favorable effect of treatment with hyperimmune rabbit serum in 52 cases of Rocky Mountain spotted fever.

In the Children's Hospital of the University of Amsterdam, Netherlands, 4 children were treated with gamma globulin. In these children the presence of a virus infection could be assumed.

The first patient was a 1½ year old boy, who had encephalitis. On the fourth day after his admission to the hospital, 5 cc. of a solution of gamma globulin was injected. The following day the temperature had fallen to the normal and no convulsions were observed from that day on. The paralyses slowly disappeared.

In the second child, a boy who had meningoencephalitis, the improvement began some hours after the injection of gamma globulin. However, this improvement may not have been due to the treatment but may only have coincided with the injection.

The favorable effect of the injection was seen in a child with diarrhea and encephalitis, in whom no pathogenic bacteria were demonstrated, and in another with virus pneumonia. The change in the general condition, the quick fall of the temperature and, in 3 patients, the cessation of the convulsions were striking in all these children.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

GENERALIZED NON-FATAL HISTOPLASMOSIS IN AN INFANT. RICHARD W. BLUMBERG, ISAAC RUCHMAN and RALPH J. JOHANSMANN, Pediatrics **3**:296 (March) 1949.

A case of systemic infection with Histoplasma capsulatum with recovery is reported. The organisms were recovered from the blood, bone marrow and liver. No specific therapy was administered. A change in cutaneous sensitivity to histoplasmin from negative in the early stage to positive in the convalescent stage was noted. No cross reactions with various other fungous antigens were observed.

FROM THE AUTHORS' SUMMARY.

PURE GRANULOMATOUS NOCARDIOSIS. MARVIN L. WEIL, JOHN T. CUTTINO and ANNE M. MCCABE, Pediatrics **3**:345 (March) 1949.

A case of an infectious granulomatous disease, in which the clinical picture resembled that of a retroperitoneal tumor, is presented. The etiologic agent is shown to be a hitherto undescribed organism, Nocardia intracellularis n.sp. The clinical similarity of this rare disease to xanthogranulomas and neoplasms is emphasized. The diagnosis rests primarily on histopathologic studies of the lesions, especially with reference to intracellular organisms. The condition may be suspected if atypical acid-fast organisms are detected in the stools of patients with clinically similar pictures.

FROM THE AUTHORS' SUMMARY.

BCG Tuberculin Studies: An Experimental and Clinical Investigation. J. Henning Magnusson and A. Lithander, Pediatrics **3**:429 (April) 1949.

A report is given on experiments embarked on in order to obtain, with the aid of a special tuberculin, a positive Mantoux reaction in infants vaccinated with BCG at an earlier stage than is possible with commercial tuberculin. Clinical experiments were supplemented with those on guinea pigs.

The tuberculin used in the experiments, the BCG tuberculin, was prepared from batches of Sauton's medium on which the BCG strain had been allowed to grow for ten to eleven days for routine production of the BCG vaccine. After the ordinary sterility tests, the potency of the BCG tuberculin was estimated by titration against commercial tuberculin in guinea pigs infected with a virulent strain of the tubercle bacillus.

Subsequently, the reaction of BCG tuberculin was compared with that of commercial tuberculin, using altogether 118 guinea pigs infected with BCG vaccine. Of either type of tuberculin, 1 and 0.5 mg., respectively, was injected into the dorsal skin of the anmials six, seven, eight, nine, eleven and thirteen weeks after infection with BCG vaccine. The reactions evoked by the BCG tuberculin tallied in appearance with ordinary tuberculin reactions. One hundred and twenty-one guinea pigs infected with virulent tubercle bacilli served as controls. These animals were given injections of BCG tuberculin and commercial tuberculin in the same manner and at the same times as the animals infected with BCG or organisms.

It emerged from the experiments that in BCG-infected guinea pigs BCG tuberculin evoked positive tuberculin reactions at an earlier stage than did equivalent amounts of commercial tuberculin. Six weeks after infection 74.4 and 44.6 per cent were positive to 1 and 0.5 mg. of BCG tuberculin, respectively, as against 9.1 and 0 per cent, respectively, to corresponding doses of commercial tuberculin. Eleven weeks after infection the ratio was 90.4 and 66.0 per cent respectively, as against 9.1 and 23.4 per cent, respectively. The guinea pigs infected with virulent tubercle bacilli showed no difference in the reactions to the two types of tuberculin. In those BCG-infected guinea pigs in which initially only BCG tuberculin had evoked positive reactions, a couple of weeks later in the major proportion responses were observed even to commercial tuberculin, which tends to show that the reaction to BCG tuberculin is specific.

BCG tuberculin was compared with commercial tuberculin in children vaccinated with BCG organisms. This was done, on the one hand, in 491 infants vaccinated during the first week of life and, on the other, in 237 children ranging in age from 1 to 10 years. In the infants the results were largely identical with those obtained in the experiments with animals, in the earlier tests responses being considerably more frequent to BCG tuberculin than to commercial tuberculin, a difference that gradually decreased. Thus, six weeks after vaccination 84.9 per cent responded to BCG tuberculin, but only 44 per cent to commercial tuberculin. After eleven weeks the ratio was 100 and 94.3 per cent, respectively. In another supplementary series comprising 810 infants vaccinated during the first week of life, the figures were practically identical. In children ranging in age from 1 to 10 years, in tests made three, four and five weeks after vaccination the BCG tuberculin evoked responses considerably oftener than the commercial tuberculin. For example, three weeks after vaccination 75.0 per cent responded to BCG tuberculin but only 10.7 per cent to commercial tuberculin. Subsequently, this difference diminished by degrees.

On reexamination of the children those initially responding to BCG tuberculin only were noted to have positive reactions also to commercial tuberculin. This

experience shows that the reaction to BCG tuberculin is specific. In the assessment of BCG vaccination BCG tuberculin seems to be preferable to commercial tuberculin. This applies particularly to the vaccination of newborn children and infants.

From the Authors' Summary.

Antagonism of Sulfonamide Inhibition by Para-aminobenzoic Acid and Folic Acid in Toxoplasma Infected Mice. William A. Summers, Proc. Soc. Exper. Biol. & Med. **66**:509 (Dec.) 1947.

Mice were inoculated with fatal doses of Toxoplasma (R.H. strain). It was found that these animals were protected by sulfathiazole sodium in concentrations of 0.15 and 0.08 per cent but not in a concentration as low as 0.03 per cent. When paraaminobenzoic acid or folic acid was added, there seemed to be no significant effect on experimental toxoplasmosis in mice. The protection afforded the mice infected with Toxoplasma by treatment with sulfathiazole sodium was nullified by the simultaneous administration of paraaminobenzoic acid or folic acid.

Hansen, Galveston, Texas.

A Tuberculin-Neutralizing Factor in the Serum of Patients with Sarcoidosis. A. Q. Wells and J. A. H. Wylie, Lancet **1**:439 (March 12) 1949.

The serum of patients with sarcoidosis can modify or even neutralize the tuberculin reaction in the skin of sensitive persons. This phenomenon is occasionally observed with normal serum and with serum from patients with other conditions that may mobilize the epithelioid cells, e. g., kala-azar. But the reaction is particularly constant with serum from patients having active sarcoidosis. It appears that the tuberculin-neutralizing factor is in the gamma globulin fraction of the serum.

Macdonald, Pittsburgh.

Streptomycin-Streptokinase Treatment of Tuberculous Meningitis. I. A. B. Cathie, Lancet **1**:441 (March 12) 1949.

The gelatinous exudate of tuberculous meningitis presents a sometimes impenetrable barrier to streptomycin. Cathie combined the intrathecal administration of streptomycin sulfate with streptokinase to penetrate this barrier. Of 19 patients treated in this way 11 (58 per cent) recovered, compared with 14 patients treated with streptomycin alone of whom 3 (21 per cent) recovered.

Macdonald, Pittsburgh.

Tuberculous Cervical Meningitis. I. Flesch and C. Péró, Paediat. Danub. **2**:83 (Feb.) 1949.

According to clinical signs and composition of the cisternal cerebrospinal fluid, a patient with tuberculous meningitis showed almost complete recovery, when he suddenly died from peripheral respiratory paralysis due to cervical strangulation by meningeal adhesions. The adhesions were caused by a tuberculous process. Tuberculous dissemination on the meninges was most pronounced in the cervical area; basilar changes were insignificant. The usual course of the condition already indicated a diagnosis of tuberculous cerebrospinal meningitis. The supposition was fully confirmed by the changes seen at autopsy.

From the Authors' Summary.

CARBOHYDRATE METABOLISM OF PATIENTS WITH TUBERCULOUS MENINGOENCEPHALITIS TREATED WITH STREPTOMYCIN. L. BARTA, J. POZSONYI and G. SZOLNOKI, Paediat. danub. **2**:93 (Feb.) 1949.

The lability of carbohydrate metabolism is best characterized by blood sugar curves following double dextrose tolerance tests. The Staub-Traugott effect was negative in most instances. Many patients revealed pathologically steep, irregular curves with several peaks. On consideration of the pathologic encephalographic results, it is supposed that the changes of the carbohydrate metabolism in these patients were due to functional disturbances of the primary regulatory center, the diencephalon.

FROM THE AUTHORS' SUMMARY.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. W. VAN ZEBEN AND OTHERS, Maandschr. v. kindergeneesk. **16**:184 and 192 (June); 211, 217 and 237 (July) 1948.

Various Netherland clinics have published their experiences with streptomycin therapy in tuberculous meningitis. Each clinic had its own method of treatment.

In the children's clinic in Utrecht, the scheme of Cocchi was followed. For four weeks the patient received intramuscularly 20 mg. of streptomycin per kilogram of body weight per twenty-four hours, and then for forty to sixty days 15 to 50 mg. intrathecally daily. After that, for thirty to sixty days one intrathecal injection was given every other day, and thereupon the intervals between the injections became longer. Moreover, during the first two to three weeks a daily intravenous injection of 0.4 to 1.3 Gm. of diaminodiphenylsulfone was given. An infant who fell ill at the age of 8 months seemed to be cured after an observation time of ten months; a girl, 6 months old, is still being treated for a relapse.

The infectious disease department of the Wilhelmina Gasthuis in Amsterdam treated its patients in the following way: Children of the ages from birth to 7 years received 250 to 500 mg. of streptomycin intramuscularly and 25 to 50 mg. intrathecally; those aged from 7 to 12 years received 0.5 to 1 Gm. intramuscularly and 50 to 100 mg. intrathecally. The treatment lasted for two to five months. Two children, aged 4 and 6 years, who were observed for eleven and fourteen months, respectively, recovered without residua. One child 2 years old, with meningitis and miliary tuberculosis of the lungs, died during a relapse four months after the beginning of the treatment. A child 15 months old at first seemed to recover with a small intelligence defect but some months later had a relapse.

In the hospital at Heerlen, 2 children died of tuberculous meningitis; the first had been treated only ten days with streptomycin given intrathecally; the second, for a still shorter time.

In Leiden, the treatment consisted of intrathecal injection of 25 to 100 mg. of streptomycin for one to two months and intramuscular administration of 0.5 to 2 Gm. for six months. Of 5 children below the age of 2 years, 4 died and 1 recovered. Of 3 children aged 2 years, 1 died, 1 had a relapse and 1 recovered but remained deaf. Three children above the age of 4 years recovered; 1 of them remained deaf.

In the children's clinic at Groningen, 3 patients were treated in different ways; the child who died had been treated only three weeks. One child recovered, with serious residua; for twenty-five days he had been treated by intramuscular injections of 65 mg. of streptomycin per kilogram of body weight per twenty-four hours. After an interval of four weeks, he received intramuscularly 40 mg. of streptomycin per kilogram of body weight per twenty-four hours for three weeks. Moreover, during the first course of treatment an intrathecal injection of 8 mg. per kilogram of body weight was given daily, and during the second course 5 mg. per kilogram

of body weight, every other day. The third patient, who recovered, received 50 mg. of streptomycin per kilogram of body weight per twenty-four hours intramuscularly for one month and 6 mg. per kilogram intrathecally daily for sixteen days. After an interval of four weeks, the injections were repeated for one week intrathecally and for seventeen days intramuscularly.

It remains to be seen in how far the recovery in the cases described as cured will be permanent.

VAN CREVELD, Amsterdam, Netherlands.

TUBERCULOUS BRONCHITIS. S. KEYSER, Nederl. tijdschr. v. geneesk. **92**:230 (Jan. 24) 1948.

Tuberculous bronchitis arises from a specific inflammation of an area of the lung localized at the periphery of the affected bronchus. The inflammation of the mucous membrane may be hematogenic, lymphogenic or bronchogenic, or may be due to a rupture into the bronchus.

In 1 case, atelectasis of the middle lobe of the right lung was observed ten months after the initial symptoms of pulmonary tuberculosis had appeared. By means of a bronchographic study a complete stenosis could be demonstrated in the main bronchus of the middle lobe. A bronchoscopic examination revealed that the bronchus contained pus and blood and that the mucous membrane was swollen and covered with necrotic material and fibrin. This material was removed, and epinephrine injected into the bronchial wall. After 1 temporary improvement, fever and coughing returned. A bronchoscopic study was repeated three times, and pus was removed. In addition, lactic acid was applied once, and at another time penicillin was instilled to combat secondary infection. The occlusion may be caused by several factors: (1) mucous or necrotic material in the lumen of the bronchus; (2) proliferation of the bronchial wall and, later, retraction of the scar tissue, and (3) pressure from the outside by a tuberculous gland.

For treatment, widening of the stenosis with drainage or pneumonectomy, lobectomy or thoracoplasty is recommended. Two cases are described to illustrate the course after surgical treatment. In these cases lobectomy was performed after a diagnosis of bronchiectasis had been made. An examination of the removed part of the lung revealed tuberculous bronchitis. In 1 case complete recovery soon followed the operation; in the other sputum which contained tubercle bacilli was produced only once after operation and the patient recovered.

These 2 cases demonstrate the problems in the diagnosis of this disease, as well as the difficulty in choosing the most suitable treatment.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

INFECTIOUS RETICULOENDOTHELIOSIS (ABT-LETTERER-SIWE). E. KNOPF, Arch. f. kinderh. **134**:129, 1947.

This is a report on 2 cases. The first was that of a girl 2 3/12 years old who was observed for fourteen months. The diagnosis of infectious reticuloendotheliosis was confirmed by observations on autopsy and by results of microscopic examination. Several features were observed during the course of the disease which are not common in infectious reticuloendotheliosis. Thus, purpura, regarded as a necessary symptom, was missing entirely. The examination of the blood revealed a hemorrhagic aleukemia with thrombopenia and with athrombia toward the end. Some symptoms, e. g., exophthalmos, deformities of the skull and hepatosplenomegaly, were surprisingly similar to those seen in Hand-Schüller-Christian disease.

The condition of the second patient, a girl 3 years old, was diagnosed as infectious reticuloendotheliosis from the clinical symptoms and from the microscopic examination of a lymph node taken for biopsy. The autopsy revealed a sarcoma, originating from the reticuloendothelium of the left renal region. The tumor was classified as "polymorphocellular reticulosarcoma." In this patient a tumor had produced the same symptoms as seen in infectious reticuloendotheliosis.

ARON, Chicago.

GENERAL THROMBOPENIA AS INDIRECT CONSEQUENCE OF A DEFICIENCY OF EXOGENOUS AMINO ACIDS. WOLFGANG NITSCH and RICHARD HEIDRICH, Med. Klin. **44**:208 (Feb. 18) 1949.

In the after-period of the war a constant diminution in the number of thrombocytes was noted in the circulating blood. This does not include cases of essential thrombopenia, of symptomatic thrombopenias or of diseases of the hematopoietic system. It is stated that a lack of essential amino acids is concerned. For instance, phenylalanine, which is necessary for the synthesis of thyroxin and epinephrine, is present in only 28 per cent of the required amount in adults and in only 25 per cent of that in young persons. An increase in the eosinophils in the circulating blood to 3.4 per cent is regarded as a result of a deficient function of the adrenal system; therefore, the thrombopenia connected with this deficiency is an indirect result of amino acid deficiency.

AMBERG, Rochester, Minn.

A RAPID QUANTITATIVE TEST IN PLACE OF THE TAKATA-ARA REACTION. MAX FRIMMER, Med. Klin. **44**:144 (Feb. 4) 1949.

The method measures the time at which, on addition of 2 cc. of Hayem's solution to 1 cc. of nonhemolytic nonlipemic blood serum, turbidity is produced in every serum at a temperature between 15 and 25 C. (59 and 77 F.). The clinical significance of the reaction corresponds very well with that of the Takata-Ara reaction and some of its other modifications, all of which indicate a hyperglobinemia. They are not specific hepatic function tests.

AMBERG, Rochester, Minn.

MODIFICATION OF ERYTHROCYTE SEDIMENTATION REACTION TO ENLARGE ITS CLINICAL SIGNIFICANCE. FRITZ SCHMITT, Med. Klin. **44**:181 (Feb. 11) 1949.

The sedimentation rate of red blood corpuscles in citrated plasma was determined as usual according to Westergren's method. Then the sedimentation rate of the blood corpuscles was determined in serum. The usual method gives information about increase in fibrinogen and globulin, the other about globulin. The values obtained with serum were always lower than those with the usual (plasma) method. The serum values are independent of the plasma values. A high plasma sedimentation rate was noted in all patients with acute febrile inflammations, together with low serum values indicating increases in fibrinogen. Patients with chronic malignant diseases gave high values with both the plasma and the serum method. Further results are omitted awaiting additional reports.

AMBERG, Rochester, Minn.

PERIARTERITIS NODOSA: DEMONSTRATION OF A VASOCONSTRICTIVE EFFECT OF THE PATIENT'S SERUM. W. D. GERMER, Med. Klin. **44**:231 (Feb. 25) 1949.

The serum of a 24 year old patient with periarteritis nodosa of seven months' duration in a dilution of 1:2.5 produced a strong vasoconstrictive effect in the Laewen-Trendelenburg frog preparation. The blood pressure had risen from 110 to 150 systolic and from 70 to 100 diastolic. It rose further to 210 systolic and 150 diastolic to become stabilized at 180 systolic and 130 diastolic. The blood for the test was taken four weeks after the elevation of the blood pressure. After removal of the proteins of the serum by means of a current of steam at p_H 5, the vasoconstrictive effect could be elicited.

AMBERG, Rochester, Minn.

ACUTE HEMOLYTIC ANEMIA (LEDERER) WITH UREMIA AND HEART BLOCK. M. KETTNER, Ztschr. f. Kinderh. **65**:1, 1947.

The author describes the case of a 12½ year old girl who suddenly showed pallor, jaundice, circulatory disturbances, subcutaneous hemorrhages and drowsiness. Blood and urobilin were noted on urinalysis and anemia, leukocytosis, normal red blood cell resistance and high nonprotein nitrogen values on examination of the blood. Edema, hypertension and severe oliguria occurred. Short wave therapy and paravertebral anesthesia showed no result, but alkalization by the intravenous route produced increased urinary flow. Pericardial friction rub, tetany and myocardial damage occurred in the course of the disease, but the patient recovered and was considered normal five months later at examination. In the discussion the author postulates that the absence of spherocytes, increased cell fragility or familial incidence spoke against congenital spherocytosis and in favor of Lederer's anemia. The cause for the oliguria is to be found in the toxic effect of protein products rather than in mechanical obstruction due to hemoglobin. Circulatory disturbances of the coronary blood vessels account for the myocardial damage. The increased potassium ion content of the serum due to erythrocyte destruction and uremic metabolic processes, as well as the therapeutic alkalization, is responsible for the tetany.

GLASER, Chicago.

PERNICIOUS ANEMIA IN CHILDHOOD. H. KADE, Ztschr. f. Kinderh. **65**:47, 1947.

In a brief review of the literature the author documents the rare occurrence of pernicious anemia in children. A 14 year old boy came under observation with complaints of pallor, anorexia, burning sensation of the tongue and paresthesias of the hands. Loss of weight, pruritus and slight jaundice were noted. Laboratory examination showed anemia, macrocytosis, leukopenia with basophilic stippling and hypersegmentation, lymphocytosis and a color index of 1.4. Gastric analysis revealed achylia without response to histamine injection. Sternal puncture proved the presence of hyperplasia and megaloblastosis. The skull showed brush-like trabeculation and early ossification of the coronary sutures. The patient responded well to injection of liver extract and administration of pepsin, hydrochloric acid and iron preparations. After considerations on differential diagnosis, the author points out the familial occurrence of subclinical cases of pernicious anemia. Kade discusses the predisposition of these patients to polyposis and carcinoma of the stomach and recommends routine roentgenologic examinations of the gastric mucosa in patients with pernicious anemia to permit early diagnosis of pathologic changes.

GLASER, Chicago.

POPULARITY AND PREFERRED METHOD OF MICRO DETERMINATION OF THE ERYTHROCYTE SEDIMENTATION RATE. F. KÜSTER, Ztschr. f. Kinderh. **65**:175, 1947.

Among the macrodeterminations of the erythrocyte sedimentation rate the Westergren method is most popular. The difficulties of venipuncture in infants make the teaching and use of a micromethod desirable. Among 16 clinics about one third used only the macromethod (Westergren), one third only a micromethod and one third both methods. The method described by Pantschenkoff is most widely used. A pipet 20 cm. long with a diameter of 1 mm. is used; 25 mm. from the point a scale of 100 mm. starts. A 5 per cent sodium citrate solution is drawn to the lower end of the scale. Five to eight drops of blood from the finger tip are collected in a watch glass, drawn into the pipet up to the upper end of the scale and mixed with the citrate solution in another glass. A column of 10 cm. of the mixture of citrate solution and blood is drawn into the pipet and observed after one hour. Normal sedimentation rate is considered to be up to 8 mm. The findings of other authors are reported in table form and seem to substantiate the accuracy of this method. The author recommends more extensive teaching of this method by children's clinics.

GLASER, Chicago.

BANTI'S DISEASE (SPLENOMEGALY OF UNDETERMINED ORIGIN). DAG RIIS, Tidskr. f. d. norske lægefor. **66**:82 (Feb. 15) 1946.

Two cases are reported of splenomegaly in children. The first patient, a boy 7 months old who had had dyspeptic symptoms for two months, became ill with melena during a febrile state considered to be due to acute pneumonia. The day before the bleeding splenomegaly was demonstrated; the day after the bleeding, the size of the spleen was decidedly decreased. The temperature remained elevated temporarily, and the condition was variable. At 11 months of age a new attack of melena occurred. Later, severe hematemesis and more continuous bleeding from the bowels took place. He died at home shortly afterward. No postmortem examination was done. In addition to the aforementioned symptoms, he displayed signs of ascites, esophageal varices (roentgenologic diagnosis) and anemia of secondary type, with no leukocytosis.

The second child was a boy, aged 13 months when first seen. During the first months of life he had had pyoderma, pneumonia and bronchitis. Splenomegaly was observed at about 7 months of age. When seen, he was pale, with hypotonia and pronounced splenomegaly. The hemoglobin concentration was 60 per cent; white corpuscles numbered 2,300 to 6,000 and thrombocytes from 100,000 to 190,000. The bone marrow showed hyperactive erythropoiesis and no Gaucher cells. No varices of the esophagus were demonstrable. Splenectomy was performed. The spleen showed hyperplasia and fibrosis. Hematemesis and melena occurred shortly after the operation, then uneventful recovery. He was discharged from the hospital in good condition.

WALLGREN, Stockholm, Sweden.

HYPERCHROMIC ANEMIA TREATED WITH FOLIC ACID. ARNE NJÅ, Tidskr. f. d. norske lægefor. **66**:738 (Dec. 1) 1946.

A boy, 10 years old, had displayed hyperchromic anemia since 1½ years of age, when he had had dyspeptic symptoms without steatorrhea. There were no megaloblasts in the bone marrow, and the gastric juice contained hydrochloric acid. The hemoglobin concentration was 40 to 60 per cent and the color index 1.15 to 1.3. No enlargement of spleen or liver was noted. There was a constant albuminuria

without other signs of renal disease. Liver therapy given parenterally had sometimes produced satisfactory regeneration. When last seen, he did not react to treatment with liver. The hemoglobin concentration was 50 per cent; red blood corpuscles numbered 2,260,000. The color index was 1.15, with 2 reticulocytes per thousand cells. White blood cells were 6,400. No normoblasts or megaloblasts were seen. Serum iron measured 183 micrograms per hundred cubic centimeters. Rapid regeneration was observed after treatment with folic acid. In the first week the dose was 15 mg., and from the second week 10 mg. was given daily. At the same time, the distinct, rapid improvement of the general condition of the boy was noted.

WALLGREN, Stockholm, Sweden.

PURPURA FULMINANS. SVEN HEINILD, **Ugesk. f. læger 108**:1370 (Dec. 5) 1946.

A previously healthy 3 week old breast-fed infant became ill suddenly with rapidly increasing symptoms and signs of severe toxicity, including blue-black, rounded purpuric spots. He died forty-six hours later. At the postmortem examination hemolytic streptococci were recovered from the cutaneous lesions, liver and abdominal fluid. The author is of the opinion that purpura fulminans most often or always is due to streptococcic septicemia and recommends as treatment large doses of chemotherapeutic compounds and penicillin.

WALLGREN, Stockholm, Sweden.

PERIPHERAL CIRCULATORY DISORDER AS INITIAL SIGN IN ACUTE LEUKEMIA IN CHILDHOOD. TAGE ESPERSEN and SVEN KIÄR, Ugesk. f. læger **108**:1453 (Dec. 26) 1946.

A girl, 9 years of age, was first seen eight days after onset of illness with sudden pains in her feet and legs. At the examination, the right foot was livid and there was no pulsation in the corresponding dorsalis pedis and popliteal arteries (oscillometric examination). A tentative diagnosis of thrombosis of the right popliteal artery was made. Examination of the blood revealed anemia and leukopenia, with a preponderance of lymphocytes and myelocytes. A biopsy specimen of the bone marrow showed abnormal mononuclear cells. At the postmortem examination the final clinical diagnosis of acute leukemia was confirmed.

WALLGREN, Stockholm, Sweden.

ARTERIAL CALCIFICATIONS IN INFANCY. INGRID LINGMARK and U. MURRAY, Nord. med. (Hygiea) **29**:183 (Jan. 25) 1946.

A male infant died at the age of 2 months after displaying symptoms of impaired breathing and attacks of cyanosis. At the first examination a few hours before death, there were an intense dyspnea and cyanosis, enlargement of the heart and liver and roentgenologically demonstrable calcification of arteries in the axillas. The postmortem examination revealed extensive calcification of the media, as well as thickening of the intima, in the visceral and peripheral arteries. The coronary arteries were the most affected vessels, and the heart was considerably enlarged. No generalized calcium deposits were observed in the organs. The parathyroids and the skeletal portions of the body were unaffected. The disease, in the opinion of the authors, was a dystrophy of the structures of the arterial walls which gave the vascular tissue an increased affinity to calcium deposits. The parents were healthy and the Wassermann reaction negative.

WALLGREN, Stockholm, Sweden.

ANGIOCARDIOGRAPHY: KNOWLEDGE NECESSARY TO MASTER ITS TECHNIC AND TO RECOGNIZE ITS INDICATIONS AND RESULTS. A. CASTELLANOS, Rev. españ. pediat. **3**:23 (Jan.-Feb.) 1947.

Dr. Castellanos gives his technic for injecting iodopyracet (diodrast®) into the chambers of the heart in infants and children, including a table of dosage and concentrations for patients of various age groups. In most children he tries to use an arm vein, although at times the saphenous is used. In an injection into the external jugular a special "bayonnet-shaped" adapter is employed. The solution is injected rapidly and evenly and a plate showing the right side of the heart, i. e., a dextroangiocardiogram, is taken immediately. Two to four seconds later, by means of a plate changer, the left side of the heart is visualized on another plate. The author points out the interpretation of the plates, septal defects, intraventricular communications, pulmonary stenosis, tetralogy of Fallot, persistent ductus arteriosis and even coarctation of the aorta being defined by this method. Eight plates are presented. The author urges the use of angiocardiography in the clarification of congenital malformations and in the differential diagnosis of mediastinal shadows.

MILLER, Newark, Ohio.

Diseases of Nose, Throat and Ear

THE INCIDENCE OF CONGENITAL IMPATENCY OF THE NASOLACRIMAL DUCT. EDWIN L. KENDIG JR. and DUPONT GUERRY III, J. Pediat. **36**:212 (Feb.) 1950.

Congenital impatency of the nasolacrimal duct was found in 5.7 per cent of 1,000 newborn infants. In most of these patients the condition cleared with local application of penicillin, ophthalmic ointment and massage of the lacrimal sac. If patency has not been established by the age of 6 months, the duct should be probed.

MACDONALD, Pittsburgh.

HEARING DEFECTS IN CHILDREN. LAVELL H. LEESON, Canad. M. A. J. **62**:167 (Feb.) 1950.

The author points out the necessity for early recognition and treatment of the deaf child. One who becomes deaf prior to 2 years of age will not be able to learn speech. One who becomes deaf at 2 years of age is amenable to treatment, and this fact should lead physicians to take advantage of all methods available, including surgery and radium. Training is highly important, both for the child and for the parents, and should be emphasized. The children should be kept in the home rather than institutionalized.

MCGUIGAN, Evanston, Ill.

DIFFICULT TEETHING AS A CAUSE OF SINUSITIS. ROBERTO L. SANCHEZ, Bol. méd. d. hosp. inf., Mexico **6**: 37 (Feb.) 1949.

Sanchez explains by logical steps how sinusitis may be caused by difficult teething. First, difficult dentition produces pain; in order to prove this statement, the author presents a series of logical physiologic facts and cites several authors. Second, fear is brought about by pain; this step is also proved. Fear, says the author, turns to anger when the cause that produces fear cannot be removed. Anger, explains the author, brings about a series of complicated physiologic responses that prepare the organism to fight, since this is the only logical reaction that the id has to any change that antagonizes it. Also, the nose of an angry person suffers changes characterized by congestion, hypersecretion and obstruc-

tion. The last step does not need much proof, because it is an everyday observation that rhinorrhea and nasal obstruction may lead to sinusitis, especially in infants.

FROM THE AUTHOR'S SUMMARY.

NEW METHODS FOR EXAMINATION OF AUDITION. E. LÜSCHER, Bull. d. Schweiz. Akad. d. Med. Wissensch. **6**: 177 (March) 1950.

During recent years, otologists have devoted a growing interest to non-inflammatory diseases of the labyrinthine capsule (otosclerosis) and of the internal ear, as well as to affections of the acoustic nerve and its central pathways. This is explained, on the one hand, by the enormous increase in cases of war deafness and, on the other, by the progress made in fenestration. Moreover, the classic methods using tuning forks, acoustic bars and monochords have been shown, little by little, to be inadequate for precise topographic diagnosis of diseases of the internal ear and acoustic pathways. In addition, it also appears that classic theories regarding conduction and perception disorders do not correspond entirely to the facts. Audiometry took the first step forward when it raised acoumetry to the level of an exact method. A detailed description of this method is given, supported by a number of audiograms. However, it is only rarely that tonal audiometry alone can allow a more precise topographic diagnosis than the use of tuning forks, since the principle of these two methods is the same. This is the reason that attempts have been made to establish methods of examination based on new principles, four of which are at present in use. These are (1) the determination of the recruitment phenomenon of Fowler, (2) the measurement of the differential intensity threshold (v. Bekesy, Luscher and Zwislocki), (3) the fatigability test (Peyser, Schubert) and (4) the determination of the adaptation of the ear (Goran da Mare, Luscher and Zwislocki). These four methods are based on the properties of the auditory nervous system. By means of them it has become possible to differentiate conduction disturbances from disorders of the nervous system. In cases of diseases of the inner ear this was not possible with use of classic acoumetric methods and only rarely with use of audiometry. A review of the practical scope of the four processes is given. The results show that cases of deafness of the internal ear are due partly to a disorder of the nervous system and partly also to a disturbance of the conduction system. In any case, it is now possible by this method to confirm damage to the acoustic nerve system, which represents an appreciable step forward in the topographic functional diagnosis of auditory disturbances.

FROM THE AUTHOR'S SUMMARY

CHRONIC MAXILLARY SINUSITIS. G. M. H. VEENEKLAAS, Helvet. paediat. acta **5**:76 (March) 1950.

Chronic maxillary sinusitis is a common affliction of childhood. Of 1,327 new patients who were examined in 1948, 80 (6 per cent) showed an involvement of one or both sinuses. The condition may produce fundamentally different symptom complexes. In one instance it may lead to general complaints such as lassitude, irritability, failure at school, bad complexion and subfebrile temperature. In another group of cases the complaints tend to simulate other otorhinolaryngologic conditions, such as adenoid facies and otitis. In a third type of cases attention may be directed toward the lungs on account of a persistent nocturnal cough and adventitious bronchial sounds. Roentgenologic examination is indispensable for the diagnosis of the condition. Therapy consists in fresh air, administration of penicillin and irrigations of the antrum, with satisfactory results.

FROM THE AUTHOR'S SUMMARY.

Diseases of Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS: REPORT OF FOUR CASES IN BROTHERS. A. A. H. GAILEY, Brit. M. J. **1**:100 (Jan. 17) 1948.

The author reports 4 cases of congenital hypertrophic pyloric stenosis in brothers. The birth dates of the children were March 29, 1939, June 9, 1941, July 30, 1943 and Feb. 6, 1947. All these patients received the Ramstedt operation successfully and are, at present, in good health. An attempt was made to trace the geneologic tree, and the author states that "in this family the condition appears to have been transmitted as a Mendelian recessive character."

BIRDSONG, University, Va.

MORTALITY FROM APPENDICITIS IN SCOTLAND, 1901-45. J. B. DEW. MOLONY, Edinburgh M. J. **55**:153 (March) 1948.

The word appendicitis was coined by Fitz in 1886 but was not used in mortality statistics in Scotland until 1901. The author studied the 17,701 registered deaths from appendicitis from then until 1945. He found that mortality is higher for males than for females. The lowest mortality is found in the age group under 15 years, the highest in the age group over 55 years.

MACDONALD, Pittsburgh.

THE BLOOD AND BONE MARROW IN THE SPRUE SYNDROME. ELIZABETH M. INNES, Edinburgh M. J. **55**:282 (May) 1948.

Innes studied 63 patients divided as follows: 17 adults (9 men, 8 women) with tropical sprue; 27 adults (21 men, 6 women) with nontropical sprue, and 19 adults (5 men, 14 women) with celiac disease. Those with tropical sprue consistently showed macrocytosis without severe anemia. Severe anemia was more prominent in patients with nontropical sprue. Macrocytosis was prominent but, in contrast with the observations in tropical sprue, blood smears showed fully stained macrocytes with hypochromic microcytes in varying proportions. Considerable numbers of target cells were present. Four patients with nontropical sprue showed hypochromic normocytic anemia.

When macrocytosis was present to a notable degree, both patients with tropical and those with nontropical sprue showed megaloblastic bone marrow. The marrow could be altered to a normoblastic or "intermediate" state by parenteral liver therapy, but the blood picture was rarely restored to normal by such treatment. It seems that sometimes, but not always, treatment with folic acid may relieve the macrocytosis after liver therapy has failed.

The characteristic blood picture of celiac disease showed hypochromic microcytic anemia, with the frequent appearance of target cells. The bone marrow was normoblastic in the 2 children in whom such studies were made. One patient with nontropical sprue had a history suggestive of celiac disease in childhood and 4 patients with nontropical sprue showed dwarfing of the skeleton. The author, however, is of the opinion that the difference in sex incidence is evidence against the idea that nontropical sprue may be a continuation of celiac disease.

MACDONALD, Pittsburgh.

CONGENITAL HYPERTROPHIC STENOSIS OF THE PYLORUS: A HISTOPATHOLOGIC STUDY. G. NIERO, Clin. pediat. **29**:13 (Jan.) 1947.

On the basis of a histologic study on the pyloric tissues of a 4 month fetus and of 5 patients with pyloric stenosis, Niero interprets the pyloric malformations as

due to (1) arrest of development in the antral portion which retains the typical fetal structure and (2) hypertrophy and hyperplasia characterized by local growth not only of the muscle coats but also of the nervous elements.

HIGGINS, Boston.

DIAGNOSIS AND TREATMENT OF PNEUMOCOCCIC PERITONITIS IN INFANCY. L. Rocco, Lattante **19**:246 (April) 1948.

An infant 2 months of age had primary pneumococcic peritonitis with edema of the scrotum and tunica vaginalis and retraction of the testes. The diagnosis was established when a laparotomy was done for a suspected appendical abscess. Treatment was with penicillin, a total of 1,500,000 units being given over a period of fifteen days. The child was discharged from the hospital as well on the sixteenth day and when seen three months later was in perfect health.

HIGGINS, Boston.

BONE MARROW IN CHILDREN WITH ULCERONECROTIC LESIONS OF THE ORAL CAVITY. G. ROBERTO BURGIO, Pediatria **56**:15 (Jan.-March) 1948.

The object of this study was a determination of the cellular composition of the bone marrow of 14 persons with ulceronecrotic lesions of the oral cavity; 2 had a noma and 12 an ulceronecrotic stomatitis (Plaut-Vincent) with lesions of various extension and depth. In each of them the blood picture was simultaneously determined. The more prominent alterations affecting the bone marrow involved the granulocytic series. A conspicuous hyperplasia of the granulocytic series, often with anaplasia, was observed, particularly in 2 of the patients with the illness (1 with noma). This was determined from the elevation in the polymorphonuclear leukocytes and from the variations in the maturation index. The curves for mitosis of the white cells in 8 cases showed a distinct stimulus. Except for some alterations in cell maturation, irregularities of erythopoiesis were not observed.

FROM THE AUTHOR'S SUMMARY.

ULCERONECROTIC STOMATITIS TREATED BY PENICILLIN. V. BAFFI, Pediatria **56**:314 (April) 1948.

The conditions of 6 children with severe ulcerative stomatitis from various primary causes—although 5 had Vincent's angina—responded to penicillin therapy, the average total dose being 510,000 units.

HIGGINS, Boston.

CLINICAL AND ROENTGENOLOGIC FINDINGS IN CHILDREN OPERATED ON FOR CONGENITAL HYPERTROPHIC STENOSIS OF THE PYLORUS. D. AGOSTO and C. DE MARCHI, Pediat. med. prat. **23**:29 (Feb.) 1948.

A report is made on the results of examination in 25 children who had been operated on for pyloric stenosis by the Fredet-Ramstedt-Ombrédanne method ten months to twelve years previously. The operation was successful in relieving the symptoms of pyloric obstruction and spasm in each case, and the children appeared to have normal growth and nutrition. Roentgenologic examination revealed that the pyloric canal was of normal length and caliber in 17 children; in the others, it was longer and narrower. The emptying time of the stomach after a barium sulfate meal was normal in 20 children and more or less retarded in 5.

HIGGINS, Boston.

GLYCOGENOSIS (VON GIERKE'S DISEASE). U. VIGNOLO LUTATI, Pediat. med. prat. **23**:77 (April) 1948.

A twenty-four page review and discussion on the present knowledge of glycogenosis is presented.

HIGGINS, Boston.

IMPORTANT POINTS IN THE TREATMENT OF ACUTE DIARRHEA IN INFANCY. E. NASSAU and J. DEUTSCH, Schweiz. med. Wchnschr. **78**:547 (June 5) 1948.

The treatment of the acute diarrheas in infancy has been much simplified recently. This applies to the so-called alimentary disturbances, also to all nonspecific intestinal infections and to the alimentary disorders caused by dysentery bacilli. The use of the sulfonamide preparations has also simplified the dietetic regimen previously practiced. The use of this medicinal treatment has made it possible to resume a normal quantitative and qualitative diet after a few days' treatment. The therapeutic advances find expression in the lower mortality, particularly from the so-called toxicoses. The mortality in this condition fell from 50 to 60 per cent to 5 per cent. The simplification of the diet led to the omission of the "nutritional cure" food (like protein milk, buttermilk, defatted breast milk). Nowadays, half milk with sugar added and rice water or corn flour may be used in even the severest cases with good results. Lactic acid milk is useful in some cases. On the average most children after the third day can receive sufficient food to cover their caloric needs. Even in the severest cases of diarrhea in young infants the disease as a rule yields in one to one and a half weeks. The authors in treating the alimentary dyspepsias and intoxications and nonspecific intestinal infections use sulfathiazole. They find this superior to sulfaguanidine, though they are of the opinion that in true dysentery, when bloody mucous stools occur and when the disease is confined to the large bowel, the slowly absorbed sulfaguanidine is preferable. The latter drug should be administered in the strength of 0.3 Gm. per kilogram of body weight.

ABT and ABT, Chicago.

Nervous Diseases

TREATMENT OF INFANTS' PURULENT MENINGITIS WITH PENICILLIN AND STREPTOMYCIN. I. VINCE, Paediat. danub. **4**:9 (July) 1948.

Thirty-five infants with purulent meningitis were treated with penicillin and streptomycin. The following conclusions can be stated on the basis of the observations.

Early diagnosis and early identification of the micro-organism are essential factors in therapy. Therefore, when suspicion arises, a lumbar puncture should immediately be performed. The cerebrospinal fluid should be examined both in smears and on culture mediums.

During infancy, purulent meningitis, from the point of view of therapy, is to be considered a septicemia. Antibiotic drugs should be given intramuscularly and intrathecally, and every disturbance in physiologic balance should be restored (acidosis, dehydration, hypoproteinemia, anemia, disturbed circulation, cerebral edema). For this reason, sulfonamides, plasma transfusion and other additional therapeutic methods are to be used.

The dosage of penicillin or streptomycin depends on the severity of the infection and the resistance to the agent. The resistance should be determined in every case. If this is impossible, higher doses than are apparently needed should be given. Therapy must not be terminated before all symptoms point to recovery. If these principles are observed, the prognosis of purulent meningitis of infants

becomes favorable. Of the 35 infants, 23 recovered and only 12 died. The death of 6 patients was clearly due to shortage of the drugs. In 1947, when antibiotic drugs were available in sufficient quantity, only 3 of 22 patients died. Their conditions all belonged to the "sterile" group. If it was possible to recognize the agent and adequate therapy could be instituted, the patients invariably recovered.

FROM THE AUTHOR'S SUMMARY.

SIGNIFICANCE OF SPINAL RELEX OF GALANT IN INFANTS. I. FLESCH, Paediat. danub. **4**:37 (July) 1948.

The fact that the spinal reflex of Galant can be elicited from organs situated in the reflexogenous zone at some distance from the body surface may have diagnostic value. Painful stimuli accompanying inflammation lead to characteristic tonic postures. These make it possible to recognize processes far below the surface. In order to demonstrate this, the author reports the case of an infant with tuberculous meningitis. The posture shown in the figure included in the study was taken up suddenly and persisted for a month. The probable peripheral origin of the reflex posture was a circumscribed collateral edema of the skin of the abdomen. The ultimate diagnosis, splenitis and perisplenitis, could not be confirmed before autopsy. The permanent contracture of the coxal region resulting in a subluxation of the pelvis is not typical of the Galant posture. The appearance of the Galant reflex points to the relation of the spleen to the reflexogenous zone, and it may be characteristic of inflammatory processes of the spleen.

FROM THE AUTHOR'S SUMMARY.

BRAIN TUMOR IN CHILDREN. B. NYRIN, Nord. med. **35**:1566 (July 18) 1947.

Thirty-two patients with brain tumors were seen at the Children's Hospital in Götenborg, Sweden, during a fifteen year period. The nature, localization and frequency of the commonest signs and symptoms are presented in two tables. Six of the patients survived, 2 of whom were treated with roentgen irradiation (1 had pituitary adenoma with diabetes insipidus, observed eleven years, and the other had thalamic glioma diagnosed by exploratory trepanation, observed seven years). The remaining 4 patients who recovered were treated surgically (2 had astrocytoma of the fourth ventricle with observation times of six and seven years; 1 had tuberculoma of the cerebellum with five years' observation time; 1 had Sturge-Weber disease with observation time of seven years).

WALLGREN, Stockholm, Sweden.

ACCUMULATION OF CASES OF HITHERTO UNDESCRIBED TYPE OF ENCEPHALITIS. OLLE GABINUS, Svenska läk.-tidning. **44**:837 (April 11) 1947.

Among the 60 healthy infants at an infants' home 44 cases of acute infection occured during less than three weeks in January 1947, with fever and vomiting without any clinical signs of involvement of the central nervous system, with one exception. This infant displayed on the eleventh day of illness rigidity of the neck and other signs of meningoencephalitis. The spinal fluid of 6 other febrile infants was examined and showed mononuclear pleocytosis and a slight increase in the globulin content in 5. The author regards it as probable that the unexamined sick infants also had meningoencephalitis. Ten of the 30 nurses at the same time had evident encephalitis, and in addition 2 patients were suspected of having encephalitis. The institution had a separate home for 18 mothers with their newborn babies, who were cared for by 7 nurses. In this ward only 1 mother became ill

with encephalitis three weeks after the small epidemic had stopped. The nurses and the mothers had their meals in the same dining room. The milk mixtures of the infants were prepared at the milk kitchen of the nursery and the other food of the infants in the general kitchen. The author is of the opinion that origin of the epidemic as an alimentary infection is excluded and holds an air-borne infection most probable. The incubation period was a few days. In 1 patient who died encephalitic and profound vascular changes of the cerebrum, with secondary large thrombosis, were found. Bacteriologic and virologic examinations gave negative results.

WALLGREN, Stockholm, Sweden.

Psychology and Psychiatry

THE INCIDENCE OF MONGOLOID IMBECILITY IN THE NEWBORN INFANT. GEORGE F. PARKER, J. Pediat. **36**:493 (April) 1950.

The incidence of mongolism in 27,931 consecutive live births was 1.15 per thousand, a total of 32 cases. The disorder was seen more frequently in premature infants.

MACDONALD, Pittsburgh.

EFFECT OF GLUTAMIC ACID ON MENTAL FUNCTION; PILOT STUDY. WILLIAM J. KERR and S. A. SZUREK, Pediatrics **5**:645 (April) 1950.

Administration of large doses of levo glutamic acid to children of normal intelligence produced no significant change in testable intelligence as compared with those receiving a placebo (glycine and tartaric acid).

The results do not substantiate previous reports that glutamic acid will increase measurable intelligence. Attitudinal effect on the part of nurses, psychologists and psychotherapists, which might have influenced the results, was minimized by the use of careful controls and different psychologists in each test situation.

Because of the small number of cases reported, further studies are needed on larger groups with similar controls. A hospital with a large, stable population of children with low testable intelligence would be preferable to the Langley Porter Clinic. One such study is soon to be reported. The results are in essential agreement with those of Kerr and Szurek.

FROM THE AUTHORS' SUMMARY.

PEDIATRIC PSYCHIATRY. L. N. J. KAMP, Maandschr. v. kindergeneesk. **18**:29, 1950.

In this paper, the first lecture given by the author as an associate professor of child psychiatry at the University of Utrecht, the field of child psychiatry is outlined in a discussion of the following items: psychologic problems in the first year of life, preventive mental hygiene, importance of psychoanalysis and developmental psychology and relation between culture and the emotional maladjustment of children.

A description is given of the institutions necessary for an up-to-date practice of child psychiatry. Finally, the interrelations between child psychiatry and the other medical disciplines are elaborated on.

FROM THE AUTHOR'S SUMMARY.

PEDIATRIC APPRAISAL OF THE DIFFICULT CHILD. L. NISSIM, Minerva pediat. **2**:51 (Jan.) 1950.

The various habit, emotional, behavior and psychiatric maladjustments found in children are listed and a plea made for a more extensive program of study of these cases in Italy.

HIGGINS, Boston.

PSYCHOMETRY AND EDUCATION. GREGORIO B. PALACÍN, Bol. Inst. internac. am. de protec. a la infancia **24**:59 (March) 1950.

The author, a distinguished educator, has investigated the mental or psychologic tests, the educational tests, the Binet-Simon intelligence scale, the age scale intelligence quotient and Rossolimo's profile graphs. He credits each with its proper value but establishes that psychometry must be practiced by experts, aware of the individuality of their pupils, who can observe them in different moments of activity. He emphasizes that it must be never forgotten that in education it is impossible to displace the subjective element—the teacher.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

STUDIES IN CHRONIC RETENTION. CHARLES WELLS, Proc. Roy. Soc. Med. **43**:43 (Jan.) 1950.

A three year study of renal function in prostatism and other obstructive states is summarized. Principal findings are (1) intact ureter does not allow fluid to be forced upward; (2) once the ureter is dilated at its distal extremity the dilatation of the balance of the ureter and kidney pelvis with consequent hydronephrosis is an extremely rapid process; (3) failure of renal function following surgery was in all instances the result of infection as is shown by a rapid response to streptomycin; (4) blood urea levels must be determined after surgery at hourly rather than daily intervals. After surgical relief of obstruction the amount of fluid required cannot possibly be taken by mouth. Intravenous therapy is essential, as is careful control of blood pressure and maintenance of electrolytic balance.

Fourteen cases are reported with seven figures and three tables.

HEARD, Monterey, Calif.

STREPTOMYCIN FOR VULVOVAGINITIS IN CHILDREN. S. GALEOTA and G. DONATELLI, Pediatria **58**:57 (Jan.) 1950.

Five girls, 3 to 7 years of age, were cured of gonorrheal vulvovaginitis by the injection of 2 to 5 Gm. of streptomycin in doses of 0.2 Gm. every three hours. Earlier treatments with penicillin and with sulfonamides were unsuccessful.

HIGGINS, Boston.

THE TREATMENT OF UREMIC CONDITIONS WITH PERITONEAL DIALYSIS. H. HEUSSER, Bull. schweiz. Akad. d. med. Wissensch. **6**:55 (March) 1950.

A report on a patient with uremia caused by interstitial nephritis successfully treated with peritoneal dialysis is presented.

The technic, being simple peritoneal dialysis, should be applied more frequently. The greatest problem, no doubt, is the right choice of the dialyzing liquid. In order to choose the most efficient liquid, a perfect knowledge of salt and water metabolism is necessary. A permanent control of blood, urine and dialyzing liquid should be done during treatment.

A number of factors which have to be considered as very important are mentioned.

FROM THE AUTHOR'S SUMMARY.

Diseases of Ductless Glands: Endocrinology

THE USE AND ABUSE OF DESICCATED THYROID. E. KOST SHELTON, California Med. **67**:9 (July) 1947.

For many years observers interested in metabolic disorders have known that the level of oxygen consumption—as indicated by a so-called basal metabolic rate—is not a true, or perhaps one should say, not an infallible measure of thyroid function.

In addition to this fact, the technical flaws incident to the arrival at a figure representing the supposed basal metabolic level are legion. It might be well to mention again the vagaries of the patient, the machine and the technician, not to speak of such apparently minor items as the cold bed, the noisy or stuffy room and the fact that most persons have claustrophobia.

Iodine and cholesterol values, when considered alone, are subject to the same criticism, both as to the variations in the laboratory technic and the danger of dogmatic interpretation.

In childhood the bone age and the urinary excretion of creatine are also helpful in diagnosis. While bone age continues to be the most objective evidence of the developmental status of the child, not all children with retarded bone age have hypothyroidism.

IN childhood small doses of thyroid are anabolic, while large doses are catabolic. When indicated, nothing works in so spectacular a manner as thyroid in children with problems of growth and development. The most outstanding stimulation of growth obtained has been with doses ranging from 1 to 2 grains (0.06 to 0.13 Gm.) of thyroid daily. Larger doses have been advocated in cretinism, but it is the author's opinion that when 2 grains of thyroid will not rehabilitate a hypothyroid child twice that much will have no better effect. If the dose is too high, calcium will be withdrawn rather than deposited, and the patient will remain on a negative mineral balance. Here again, when the patient is not truly hypothyroid, growth will not be stimulated and thyroid is worse than useless.

Thyroid is a specific drug in hypothyroidism. The administration of thyroid to normal persons depresses thyroid function. A diagnosis of obscure hypothyroidism can be made both clinically and from the laboratory when a number of criteria are considered. Thyroid dosage in all patients, and in both children and adults, ranges from ½ grain to 3 grains (0.03 to 0.19 Gm.) a day. Small doses of thyroid probably postpone the aging process in middle-aged adults with moderately high cholesterol values. Thyroid should be administered alone until its full effect on a given subject is well established.

PRYOR, Redwood City, Calif.

COMPARISON OF THE SPERMATOGENIC AND ANDROGENIC PROPERTIES OF TESTOSTERONE PROPIONATE WITH THOSE OF PITUITARY ICSH IN HYPOPHYSECTOMIZED FORTY-DAY-OLD MALE RATS. MIRIAM E. SIMPSON and HERBERT M. EVANS, Endocrinology **39**:281 (Nov.) 1946.

The anterior pituitary control of the reproductive system of the male has commonly been assumed to be exercised through the combined action of the follicle-stimulating hormone (FSH) and the interstitial cell-stimulating hormone (ICSH). The interstitial tissue of the testis, and hence indirectly that of the accessory reproductive organs, was assumed to be stimulated by ICSH and the germinative components of the testicular tubules by FSH. The injection of follicle-stimulating extracts—especially the more purified forms—however, failed

to give adequate tubular stimulation to support this concept. Likewise, the addition of FSH to pure ICSH did not give the amount of augmentation anticipated. More disturbing still was the discovery that testosterone could stimulate the germinal epithelium of the male. As ICSH causes the Leydig cells to secrete androgen, it followed that ICSH might be the only pituitary hormone necessary for testicular function.

Therefore, a comparison was made by the authors between the spermatogenic and androgenic potencies of testosterone propionate in male rates hypophysectomized at 40 days of age and given injections for fifteen days immediately following the operation. This was done for comparison with the action of pituitary ICSH in these test animals. ICSH has been assumed to act on the testicular tubules indirectly, through the androgen produced by the interstitial cells, yet it was observed that ICSH stimulated spermatogenesis at doses far below those affecting the accessory organs of reproduction, whereas testosterone propionate stimulated spermatogenesis only at levels which were also effective in stimulating the male accessory organs.

JACOBSEN, Buffalo.

ABSENCE OF RENOTROPIC EFFECTS ON THE ADMINISTRATION OF PURE ADRENOCORTICOTROPIC HORMONE (ACTH). MIRIAM E. SIMPSON, CHOH HAO LI and HERBERT M. EVANS, Endocrinology **39**:286 (Nov.) 1946.

A renotropic action of purified adrenocorticotropic hormone (ACTH) in rats was reported by Reiss (1944). The preparation used by him contained 24 to 48 corticolipid units per milligram. A 35 per cent increase in renal weight (expressed in relation to body weight) was observed twenty-four hours after the injection of 8 mg. The gross and microscopic changes noted by Reiss pointed to injurious effects on the kidneys.

The authors attempted to reproduce these effects but concluded that pure ACTH, administered acutely in doses adequate to produce definite adrenal hypertrophy and thymic atrophy, failed to produce an increase in renal weight and had no histologically detectable effect on the renal tubules.

JACOBSEN, Buffalo.

THE ADRENAL CORTEX AND THE LYMPHOCYTOPENIA DUE TO GLUCOSE ADMINISTRATION. FRED ELMADJIAN, HARRY FREEMAN and GREGORY PINCUS, Endocrinology **39**:293 (Nov.) 1946.

Lymphatic atrophy and lymphopenia are common symptoms of the alarm reaction. The pronounced activity of the 11-oxygenated corticosteroids in inducing lymphatic regression and lymphopenia has led to the concept that the adrenal cortex, through its secretions, is a primary regulator of these phenomena. The authors employed the lymphocyte count as an indicator of adrenocortical function in normal and psychotic subjects, especially in relation to acutely stressful situations.

It has been reported that a high carbohydrate diet leads to involution of lymphatic tissue and lymphopenia. Data on human subjects indicate that the administration of glucose in the two dose Exton-Rose sugar tolerance test leads to significant lymphopenia. In this paper the authors present data indicating that the rapid lymphocytic response of animals to stress is reproduced on administration of glucose; furthermore, their data demonstrate that this response to glucose administration is mediated by the adrenal glands.

JACOBSEN, Buffalo.

ADRENAL CYSTS AND ADRENAL INSUFFICIENCY IN AN INFANT WITH FATAL TERMINATION. FREDERIC P. MOORE and ETHEL G. CERMAK, J. Pediat. **36**: 91 (Jan.) 1950.

The authors report the case of an infant with signs of adrenal insufficiency characterized by dehydration and persistent gastroenteritis and a lowered serum sodium. He was treated with desoxycorticosterone acetate and showed clinical improvement, although his serum sodium level never rose above 134 milliequivalent. He died suddenly after a minor infection at the age of 7 months. Necropsy showed bilateral adrenal cysts surrounded by normal-appearing cortical tissue.

MACDONALD, Pittsburgh.

ADRENOCORTICAL HYPOPLASIA IN THE NEWBORN INFANT. R. WILLIAM PROVENZANO, New England J. Med. **242**:87 (Jan. 19) 1950.

The author presents a case in which a newborn infant showed signs of adrenocortical deficiency shortly after birth. These signs and symptoms included listlessness, irritability, anorexia, vomiting, poor respiratory muscular action, diminished Moro reflex, grasp and sucking reflexes. There was also weight loss, dehydration, acidosis and convulsions.

Treatment with adrenal cortex extract was begun on the thirteenth postnatal day because of the persistence of the morbid signs aforementioned despite adequate treatment with oxygen and parenterally administered fluids. Clinical and biochemical improvement was noted in the succeeding ten days of treatment.

Concurrent with the discontinuance of adrenal cortex therapy in an effort to substantiate the diagnosis, the progressive evidence of dehydration, weakness and debility complicated by convulsive episodes developed, and death occurred.

Postmortem examination confirmed the clinical impression of organic deficiency of adrenal cortex tissue.

The author gives laboratory data obtained during the infant's twenty-five day span of illness and includes a brief discussion of the syndrome.

WHEELOCK, Denver.

THE HISTORY OF THE DISCOVERY OF ADDISON'S DISEASE. P. M. F. BISHOP, Proc. Roy. Soc. Med. **43**:35 (Jan.) 1950.

Bishop outlines in detail the state of knowledge of the adrenal glands from before 1849 to the present. The original description of this syndrome, by Addison, in 1849, is quoted. This description is still, one hundred years later, an outstanding medical classic. The author believes that many important and exciting syndromes have yet to be discovered and described by individual clinicians whose accuracy and thoroughness of observation will match that of Addison, Gull and Cushing.

HEARD, Monterey, Calif.

THYROTOXICOSIS IN CHILDREN. M. G. STRONK, Maandschr. v. kindergeneesk. **16**:110 (April) 1948.

There are two types of hyperthyroidism, that following a previously nontoxic goiter and Basedow's disease (toxic diffuse goiter), the cause of which is not completely understood. The latter form is infrequently seen in children. Basedow's disease occurs oftener in girls than in boys, and in 70 per cent of the patients the first signs and symptoms are encountered at about the commencement of puberty. The course of the disease in children is characterized by a greater tendency to

remissions and spontaneous cure than in adults. Preference should, therefore, be given to medical treatment of this condition in children, especially since the thyroid gland plays an important part in the development of the child. The question has arisen of the extent to which the new antithyroid drugs, especially the thiourea derivatives, are of use in the treatment of this disease in children. The thiourea derivatives inhibit the synthesis of thyroxin in the thyroid gland. The hyperplasia and hyperemia of the thyroid which develop as a result of increased thyroxin production can be prevented by the administration of iodine or small amounts of thyroid powder. Iodine promotes the action of thiouracil. This therapy can be continued for months, and after its cessation in many cases the manifestations of the disease do not return. There are, however, toxic effects of these drugs, of which the most important is granulocytopenia. The least toxic derivatives are methylthiouracil and propylthiouracil. It has also become apparent in animal experiments that prolonged administration of these drugs (for more than twenty months) is followed by a carcinogenic action on the thyroid gland. It is not possible to give a definite scheme of treatment, for there are great individual variations. The dosage must be adjusted to the basal metabolic rate, although generally not more than 400 mg. per day is given. After the basal metabolic rate has fallen to normal levels, one may carry on with a maintenance dose of, for instance, 50 mg. daily.

A girl 14 years of age was admitted to the hospital with a clinical picture typical of Basedow's disease. She was treated with methylthiouracil in a maximum dose of 300 mg. per day. The metabolic rate fell rapidly from + 25 to — 18.5 per cent, by which time the daily dose had been decreased to 50 mg. Treatment was then stopped. On account of a rising basal metabolic rate, treatment with methylthiouracil was started again two months later but leukopenia and granulocytopenia began to develop, whereon the treatment was temporarily interrupted. The further administration of small doses of propylthiouracil was followed by a rise in the basal metabolic rate to 27.9 per cent. At the parents' request and on consideration of the danger of the development of leukopenia with the larger doses of thiouracil, operation was performed. After subtotal thyroidectomy the metabolic rate was — 18 per cent, although the patient showed none of the signs of hypothyroidism. The size of the thyroid gland was not influenced by the medical treatment, however, even though the beneficial effect of iodine on the metabolic rate was apparent. A close parallelism was also observed between the fall in the basal metabolic rate and the rise in the cholesterol content of the blood.

VAN CREVELD, Amsterdam, Netherlands.

DIFFERENTIAL DIAGNOSIS OF PUBERTAS PRECOX. PH. ARONS, A. VAN ORMONDT and S. K. TENG, Maandschr. v. kindergeneesk. **17**:315, 1950.

The authors describe 2 boys presenting a syndrome of precocious puberty, caused by a carcinoma of the adrenal cortex in one and by an extragenital chorioepithelioma in the other. The diagnostic difficulties and the value of an accurate and complete hormonologic examination of the urine are pointed out.

AUTHORS' SUMMARY.

NEW EXPERIMENTS WITH REGARD TO PERORAL INSULIN THERAPY. FRITZ LASCH, Wien. klin. Wchnschr. **62**:170 (March 10) 1950.

On ultrafiltration of commercial insulin through a protein-impermeable filter a filtrate is obtained which is absorbed in the intestinal tract of animal and man and reduces the blood sugar. The filtrate amounts to about 10 to 20 per cent of the

solution. If given in the duodenum, these ultrafiltrates are resorbed rapidly, but if given by mouth the simultaneous administration of antifermentative substances, such as trypan red or malachite green, is necessary for protection of the filtrate against pepsin and trypsin. Raw, not purified, self-prepared insulin yielded more of the sugar-lowering part of the ultrafiltrate.

AMBERG, Rochester, Minn.

URINARY EXCRETION OF 17-KETOSTEROIDS BY NORMAL CHILDREN AND BY CHILDREN WITH VARIOUS ENDOCRINE DISTURBANCES. U. VIGNOLO-LUTATI and P. N. DE SARIO, Minerva pediat. **2**:45 (Jan.) 1950.

On the basis of studies on 30 normal children and 10 children with dysendocrinism the authors concluded that the urinary excretion of 17-ketosteroids affords no clearcut index to hypophysial-adrenal-testicular function.

HIGGINS, Boston.

Diseases of Muscles, Bones, Joints and Lymph Nodes

COURSE AND SYMPTOMS OF PROGRESSIVE INFANTILE MUSCULAR ATROPHY. SVEN BRANDT, Arch. Neurol. & Psychiat. **63**:218 (Feb.) 1950.

Follow-up studies on 112 cases of progressive infantile muscular atrophy in Denmark are analyzed. In one third of the cases the disease was congenital. Eighty per cent of the patients died before the age of 4 years, and only 7 lived past 15 years; all were severely disabled. Extreme hypotonia and absence of spontaneous movements were the dominant symptoms in 45 infants less than 1 year old, whereas atrophy of the proximal muscles and fibrillations were conspicuous in older patients.

McGUIGAN, Evanston, Ill.

STUDIES IN DISORDERS OF MUSCLE: III. "PSEUDOHYPERTROPHY" OF MUSCLE IN PROGRESSIVE MUSCULAR ATROPHY AND OTHER NEUROMUSCULAR DISEASES. FRANK H. TYLER, Arch. Neurol. & Psychiat. **63**:425 (March) 1950.

The "hypertrophy" of pseudohypertrophic muscular dystrophy is an involvement not of muscle but of fat and fibrous tissue. It is apparently dependent on an intact lower motor neuron, since the "hypertrophy" may develop into atrophy after damage to the anterior horn cells, as was shown in a patient of the author's in whom poliomyelitis developed.

McGUIGAN, Evanston, Ill.

OSSIFICATION OF THE METACARPAL AND METATARSAL CENTERS AS A MEASURE OF MATURATION. DORIS H. MILMAN and HARRY BAKWIN, J. Pediat. **36**:617 (May) 1950.

Ossification of the epiphyses of the first and second metacarpal and the second, third and fourth metatarsal bones occurs at fairly regular times. These bones are therefore most suitable for determining bone age between 1 and 5 years of age. Normal standards are given.

MACDONALD, Pittsburgh.

CORTISONE (COMPOUND E) AND ADRENOCORTICOTROPHIC HORMONE IN RHEUMATOID ARTHRITIS. OSWALD SAVAGE, Proc. Roy. Soc. Med. **43**:11 (Jan.) 1950.

The six known active adrenal steroids are described, with structural formulas. The pharmacology of each of three groups into which these six steroids are divided is explained and their effects compared. ACTH, apparently by causing increased

secretion of adrenal steroids in man, will produce the effects of cortisone in patients with rheumatoid arthritis. These effects are an almost immediate, dramatic improvement in symptoms and clinical signs. Savage believes that two definite points of progress have been made: 1. The progress of rheumatoid arthritis is rapidly reversible by a drug. 2. There is now a yardstick to evaluate treatment.

HEARD, Monterey, Calif.

Diseases of Eye

CHANGE AND PROGRESS IN OPHTHALMOLOGY. M. L. HINE, Proc. Roy. Soc. Med. **43**:69 (Feb.) 1950.

The most spectacular advance in recent years in ophthalmologic surgery has been the operation for detachment of the retina, followed in order of importance by intracapsular extraction of cataract, dacryocystorhinostomy, replacing excision of the lacrimal sac and corneal grafting. The latter procedure is still somewhat disappointing, but the long term successful results hold increasing hope for the future. Contact lenses and transparent plastic lenses are favorably mentioned. In operative aids, retrobulbar injections of procaine and the increased use of diathermy and radiation for intraocular neoplasms are noteworthy advances. In therapeutic measures, the sulfonamides, penicillin, aureomycin, and DFP diisopropyl fluorophosphite have been extremely successful. Ocular aids in diagnosis of brucellosis and toxoplasmosis are noteworthy.

HEARD, Monterey, Calif.

MALNUTRITIONAL KERATOCONJUNCTIVITIS. C. J. BLUMENTHAL, South African M. J. **24**:191 (March 18) 1950.

Malnutritional keratitis is the commonest cause of preventable blindness in South Africa. The author states that it is due to malnutrition of a qualitative type, since he has never seen it in a really emaciated native child. Most of the children are fat, reflecting a predominantly carbohydrate diet without vitamins. Seven clinical types are described. In the first, there is spontaneous prolapse of the iris without discernible signs in the eye to attract the attention of the parents or lay observers. Other types are due to corneal softening or liquefaction, with or without secondary infection, and acute or pseudotrachomatous keratoconjunctivitis. All the types respond spectacularly to vitamin B, even when surgery appears hopeless.

MCGUIGAN, Evanston, Ill.

OCULAR MANIFESTATIONS IN RHEUMATIC SYNDROMES, GLAUCOMA, RETINOPATHY DUE TO LIPOTROPHIC DEFECT, VIRUS DISEASES AND KERNICTERUS. V. ROSSI. Bull. d. schweiz. Akad. d. med. Wissensch. (supp. 1) **6**: 188 (March) 1950.

Modern ophthalmology, freed from the stricture and narrow limits imposed on it by exclusive specialization, continues to evolve as a true medical discipline in the service of general medicine. The pathology of a single organ forms part of general pathology, and ocular disease is considered as a symptom or an epiphenomenon of diseases of other organs and systems affected at the same time. Owing to its structure and morphologic peculiarities, the eye more readily displays subjective and objective symptoms.

Modern ideas on physiopathology are now made use of in certain ocular syndromes, although, a short time ago, the cause of the syndromes was obscure. The precise and delicate methods of biochemistry are applied to diseases of the eye, an organ which for a long time was considered as a large osmotic cell.

Senile cataract, simple glaucoma, trachoma and retinal degeneration still represent obscure etiologic problems, even though some of them have been solved by medicosurgical therapy, but, in every school, research workers are throwing themselves into more vigorous studies, even though, in their enthusiasm, they attribute to working hypotheses or theoretic premises the value of realities and certainties. Ocular diseases and syndromes, which were not recognized for a long time, have now become commonplace, thanks to the competence and perspicacity of oculists engaged in general therapeutic practice.

The pathology of the eye forms a part of general pathology; the diseases of Lindau, Sturge-Weber, Recklinghausen and Heerfordt, a wide variety of lipoid dystrophies and Marfan's disease have been given a most exact nosography. Virus and ultravirus disease, hypovitaminosis and avitaminosis and the group of diseases which includes primary anemia, leukemia and nephropathy possess and provoke a symptomatology and ocular complications which have long been attributed primarily to syphilis, tuberculosis or to idiopathies in general.

One may be satisfied with what has been accomplished and feel encouraged to persevere in an age when oculists have been able to cure detachment of the retina by surgical means, have discovered how to restore sight by means of keratoplasty and, thanks to sulfonamides, antibiotics and vitamins, have been able to treat serious visual disorders which would otherwise prove fatal.

Cutaneous Diseases; Allergy

Hemostasis in Serum Disease. M. Orlandelli, Clin. Pediat. **31**:221 (April) 1949.

Serum reactions in children usually do not affect the mechanism of hemostasis. In the cases in which purpura does occur, a combination of capillary changes and hypothrombinemia are responsible factors.

Higgins, Boston.

Effect of Biotin in Desquamative Erythroderma (Leiner-Moussous). J. Svejcar and K. Kubát, Pediat. listy **3**:5 (Jan.) 1948.

The authors analyze 87 cases of desquamative erythroderma encountered in a children's clinic from 1934 to 1947. They stress the great increase in the occurrence of the disease after World War II and the beneficial therapeutic effect of penicillin (40,000 units daily for ten to fifteen days) and biotin (0.1 to 5.0 mg. daily for five to seven days). On the basis of these observations they are of the opinion that the disease develops from both an internal cause (deficiency of biotin in the nutrition) and an external one (nonspecific infection). Combined biotin-penicillin therapy was given to 8 infants 1 to 4 months old. Seven recovered completely and 1 died of sepsis after the cutaneous disease had healed.

From the Authors' Summary.

Congenital Ectodermal Dysplasia, Caused by Herpes Infection of the Mother? S. van Crevald and C. van Waalwyk van Doorn, Maandschr. v. kindergeneesk. **16**:453, 1949.

In congenital ectodermal dysplasia a retardation occurs in the development of the ectodermal derivatives. In a boy 2½ years of age a disturbance in dental formation was noted, with insufficient growth of hair and a lack of sweat secretion. The boy had only 2 coniform teeth in the upper jaw, while on the roentgenogram any construction of teeth in the jaws appeared to be absent. Moreover, the boy had purulent rhinitis. Such a condition often is hereditary, but this child represented

a solitary occurrence. However, from an accurate anamnesis it appeared that the mother of the boy had had before pregnancy and during the first months a persistent herpes labialis. The virus of herpes simplex attacks especially the tissues of the embryonic ectoderm (skin, mucous membranes, eye, central nervous system). The authors give the opinion of Dr. T. F. McNair Scott, of Philadelphia, on the possible origin of this condition.

FROM THE AUTHORS' SUMMARY.

Teeth and Dentistry

TRILENE ANALGESIA IN PAEDIATRIC PRACTICE. J. THOMPSON, D. A. I. GREWAR and J. G. GROUNDS, Brit. M. J. **2**:1449 (Dec. 24) 1949.

Because some pediatric examinations are somewhat painful and consequently the child is uncooperative, the authors have advocated the use of trichloroethylene as an analgesic to prevent pain and to increase cooperation of the patient.

The apparatus used was the Blease inhaler, which is a simple draw-over type inhaler. The authors define analgesia as the loss of sensation of pain without the loss of consciousness, and they report a series of 60 cases representing lumbar puncture, cisternal puncture, venepuncture, burn and wound dressings and others. The patients' ages ranged from 8 months to 11 years. This analgesia was found of greatest value in children over 1 year of age, as it was relatively worthless in children under 1 year old. It is stated that the analgesia was safe and easily induced and controlled. It caused the patients no discomfort, and it took very little time to reach the condition of analgesia. It was thought that the diagnostic and therapeutic procedures could be carried out much more quickly, adequately and successfully with the use of trichloroethylene. The disadvantage of trichloroethylene was that the point at which the analgesia became effective was not easily appreciated and that there was no uniformity in response to a given concentration of trichloroethylene. The only complications noted were postanalgesic vomiting by some of the patients; otherwise there were no ill effects.

BIRDSONG, Charlottesville, Va.

FLUORINE DEFICIENCY IN WATER AND DENTAL CARIES. V. DEMOLE, Bull. schweiz. Akad. d. med. Wissensch. **6**:81 (May) 1950.

The deficiency of fluorine in drinking water is held responsible for the increase of dental caries in Switzerland, particularly among school children. As the easiest way of compensating for this fluorine deficiency, the author recommends the daily addition of 0.25 mg. of sodium fluoride (in tablets) or the fluorination of table salt.

FROM THE AUTHOR'S SUMMARY.

Miscellaneous

THE ENERGY EXPENDITURE FOR QUIET PLAY AND CYCLING OF BOYS SEVEN TO FOURTEEN YEARS OF AGE. CLARA M. TAYLOR, MINA W. LAMB, MARY E. ROBERTSON and GRACE MACLEOD, J. Nutrition **35**:511 (April) 1948.

The average results of 70 determinations of energy expenditure for quiet play and of 61 for cycling, including the cost in basal metabolism by 22 subjects, 7 to 14 years of age, are reported by Taylor and her associates. A respiration chamber equipped with a bicycle ergometer of electric brake type was used. The results are stated as the total expenditure, i. e., inclusive of the basal metabolism. Nineteen determinations were made on boys 7 and 8 years of age. With the boys

sitting quietly at play, the average energy expenditure was 3.1 calories per kilogram per hour, or 0.59 calorie per centimeter of height per hour. For cycling, the average was 6.6 calories per kilogram per hour, or 1.23 calories per centimeter of height per hour. Twenty-nine determinations of the energy expenditure in quiet play and 20 determinations for cycling were made on boys 9 to 11 years of age. For quiet play, the average expenditure was 2.6 calories per kilogram per hour, or 0.58 calories per centimeter of height per hour; for cycling, 5.1 calories per kilogram per hour, or 1.15 calories per centimeter of height per hour. Twenty-two determinations made on boys 12 to 14 years of age were for quiet play; the average was 2.1 calories per kilogram per hour, or 0.58 calorie per centimeter of height per hour; for cycling, 4.5 calories per kilogram per hour, or 1.24 calories per centimeter of height per hour. It will be noted that, whereas energy expenditure for each activity in calories per kilogram per hour decreases with the increase in age, there is practically no change when it is expressed in calories per centimeter of height per hour. On comparison of the total cost of quiet play with the basal energy expenditure, the percentage increase for the 7 to 8 year old boys was 55 per cent; for the boys 9 to 11 years, 63 per cent, and for the 12 to 14 year old boys, 62 per cent. For cycling, the increases above the basal metabolism were, respectively, 230, 219 and 246 per cent.

FREDEEN, Kansas City, Mo.

SOME PEDIATRICIANS' VIEWS CONCERNING PROBLEMS OF HANDICAPPED CHILDREN. WILLIAM MCPEAK, Pediatrics **1**:214 (Feb.) 1948.

Samples of two categories of pediatricians, professors and practitioners, gave their opinions in a recent mail survey concerning the problems of handicapped persons. Both groups revealed an awareness that many important needs of the handicapped are still unmet and that greater, more imaginative efforts are required.

The biggest obstacle to relief for the handicapped is the imperfect understanding of etiology. Comparably serious is the lag, after its accumulation, in the dissemination of scientific knowledge. A third need, that for personnel and facilities, was recognized by the pediatricians but was deemed less important because (1) many handicaps are irreversible and the problems can be solved only through basic research and (2) an expansion of government health services is expected which is more likely to provide material facilities than new scientific knowledge and education.

The pediatricians were further agreed on the following points:

1. Among handicapped children the problems demanding most attention are rheumatic fever, cerebral palsy and related disorders, mental conditions and emotional disturbances and epilepsy.

2. Poliomyelitis and other visible orthopedic conditions, with the exception of cerebral palsy, are receiving disproportionately greater attention than the invisible and nonorthopedic disorders, such as heart disease.

3. Tax-supported health activities can be expected to expand, and the proper role of voluntary health agencies will lie more and more in the field of prevention, through research, demonstration and education, and less in the actual treatment of handicapped persons.

When asked which diagnostic or symptomatic groups resulted in the greatest unmet needs, 60 per cent of the practitioners mentioned rheumatic fever. Cerebral palsy and related disorders received the second greatest emphasis, being mentioned by 42 per cent of the respondents. The third most frequently mentioned set of needs was that of children with mental problems. The needs of those with

psychiatric problems, problems in adjustment and emotional disturbances, excluding mental deficiency and epilepsy, were emphasized by 30 per cent. Most references were to those children not handicapped physically. Epilepsy was considered next most important, being mentioned by 20 per cent of the pediatricians. (Percentages total more than 100 per cent because some respondents gave emphasis equally to the needs of more than one group.)

Concerning the most effective approaches to the solution of handicapping problems, opinions tended to differ in accordance with the pediatricians' specialties, the main difference being between professors and practitioners. In general, it was found that: 1. Professors were relatively more concerned about needs for basic research and education in handicapping diseases, while practitioners seemed more impressed by shortages of facilities for direct care and treatment of individual patients. 2. Practitioners tended to the opinion that if needed care is provided for individual persons, research "will follow"; that is, problems will arise in connection with direct service which will provide opportunities for and which will stimulate the study of underlying causes. Professors tended toward the opposite view, pointing out that the most basic problems in the handicapping diseases can be formulated clearly now, and that successful research demands a systematic approach and diligent work under controlled conditions which do not automatically stem from programs of treatment.

FROM THE AUTHOR'S SUMMARY.

SALICYLATE TOLERANCE AND TOXICITY IN CHILDREN. EMANUEL DUBOW and NATHANIEL H. SOLOMON, Pediatrics **1**:495 (April) 1948.

Therapy in rheumatic fever with massive doses of salicylates has come into common use within the past few years, but there have been some differences in recent reports regarding tolerance of these drugs by children.

In this study a group of 19 children ranging in age from 8 months to 11½ years were given sodium salicylate and acetylsalicylic acid in doses of 0.150, 0.125 and 0.10 Gm. per kilogram of body weight. Serum salicylate levels, carbon dioxide content and p_H values were measured, and the patients were carefully observed for signs of toxicity, most important of which were hyperpnea, lassitude, anorexia and tinnitus. Serum salicylate levels rose above 35 mg. per hundred cubic centimeters of blood; serum p_H values rose at first and then fell, and serum carbon dioxide content fell at first rapidly and then more gradually. Acetylsalicylic acid appeared to be more toxic than sodium salicylate. Doses of 0.10 Gm. per kilogram of body weight were given, but blood salicylate levels obtained were lower than desired, ranging from 19 to 21 mg. per hundred cubic centimeters of blood. When doses of 0.125 Gm. were given, serum salicylate levels rose above 35 mg., and the p_H value and carbon dioxide content remained normal over extended periods of time.

Sodium salicylate in doses of 0.125 Gm. per kilogram of body weight appears to be the drug of choice in massive therapy. Patients should be carefully observed for the aforementioned early signs of toxicity. If these appear, blood studies and, especially, estimation of p_H values should be done. Alkali should be administered only when p_H value is low, regardless of carbon dioxide content. The latter may merely be low as a result of "blowing off" because of the salicyl-initiated dyspnea.

Since salicylates are primarily excreted through the kidney and may have a toxic effect on this organ in high concentrations, every effort must be made to maintain good renal function in cases of salicylate toxicity.

FROM THE AUTHORS' SUMMARY.

Book Reviews

Problems of Early Infancy: Transactions of the Second Conference. Second Conference on Problems of Early Infancy, New York, 1948. Edited by Milton J. E. Senn, M.D. Price, $1. Pp. 120, with no illustrations. New York: Josiah Macy Jr. Foundation, 1949.

This booklet is a report of the transactions of a conference sponsored and conducted by the Josiah Macy Jr. Foundation. The invited participants consisted of approximately twenty-five investigators prominent in the fields of pediatrics, obstetrics and psychiatry.

Almost half the book is devoted to the prenatal influences of maternal physiologic and psychologic states on the fetus and the subsequent effect on the behavior of the newborn. The concepts of prenatal influences are older than recorded history, but an objective study of them in the light of recent knowledge concerning psychosomatic relationships opens a vast field for research on the newborn. The papers and discussions which constitute this report typify a recent trend of the application of psychoanalytic concepts to clinical pediatrics.

The individual papers are of such diverse material and the discussions of them appear in such brief abstracted form that a comprehensive review of them is impossible. To choose but a few of the titles: "Emotional Factors in Eary Pregnancy," "Mental State of Women and How that State Affects the Child in a Psychosomatic Sense," "Clinical Experiences and Observations on the Use of Relaxation Methods in Obstetrical Practice" and "A Memorandum on Emotional Disorganization in this Culture" convey the wide scope of the material discussed at the conference. The booklet makes for interesting, stimulating and provocative reading.

Thyroid Function as Disclosed by Newer Methods of Study. By J. H. Means, M.D.; A. Albert, M.D.; E. B. Astwood, M.D., Ph.D.; I. L. Chaikoff, Ph.D., M.D.; E. W. Dempsey, Ph.D.; E. D. P. DeRobertis, M.D.; E. D. Goldsmith, Ph.D.; C. P. Leblond, M.D., Ph.D., D.Sc.; D. A. McGinty, Ph.D.; R. W. Rawson, M.D.; E. P. Reineke, Ph.D.; W. T. Salter, M.D., and A. Taurog. Annals of the New York Academy of Sciences, volume 50, article 4. Price, $3. Pp. 229, with illustrations. New York: New York Academy of Sciences, 1949.

This conference on thyroid function as disclosed by newer methods of study was held by the Section on Biology of the New York Academy of Sciences on Jan. 24 and 25, 1947.

Contributions to these newer methods of study include a phylogenetic consideration of the thyroid gland, cytologic and cytochemical bases of thyroid function, chemical cytologic aspects, the metabolic circuit of thyroid hormone, the formation of organically bound iodine compounds in the thyroid gland and their appearance in the plasma as shown by the use of radioactive iodine, absorption and utilization of iodine under the influence of certain goitrogens, action of various antithyroid compounds, study of metabolism of thyroxin, formation of thyroxin and the biochemistry of thyrotropic hormone and the physiologic reactions of the thyroid-stimulating hormone.

Participants in the conference discussed the various technics that have been developed and utilized in more recent research into the physiologic characteristics of this organ and presented the more significant results of their individual investigations in relation to those of others.

For those who are engaged in some of the intensive studies now being carried on in a number of centers, the volume contains a résumé of the most important contributions of workers in the field of physiology of the thyroid gland. At the same time it offers a lucid summary for the clinical and casual reader who is interested in the basic scientific accomplishments on which are founded newer methods of treatment of disorders of the thyroid gland.

Although the data included in this volume are available in original form in articles of the various contributors noted in the bibliography; the compilation and summaries in a single volume are especially useful.

Medical Meeting. By Mildred Walker. Price, $3. Pp. 280, with no illustrations. Harcourt, Brace & Company, Inc., 383 Madison Ave., New York 17, 1949.

This might be your story or mine. After twelve years as a physician in a small sanatorium for tuberculous patients, to which Dr. Henry Baker had gone directly from medical school because it offered him a chance to work, a salary on which he could support his wife and child and time for research, he is ready to present his paper on his discovery of a new life-saving mold, microcydin. You will recognize the locale of the meeting and meet your own friends with the Bakers at the conference. Everything that happens to them probably has happened to you, but less dramatically—or so it seemed at the time—because no one was there to help you see anything but the disappointment and the problems.

The laity love this "love story," revel in its showdown of medical life and its problems and laugh at the discouragements. If you have a small private tear, do not think you are alone. Many of us have had similar problems and can, with Henry, thank God for an understanding partner like Liz. The action takes place in a very few days—but therein is compressed a lifetime of effort and sacrifice.

Diagnostic Tests for Infants and Children: Principles, Clinical and Laboratory Procedures. By H. J. Behrendt, M.D. Price, $7.50. Pp. 529, with 45 figures and 76 tables. Interscience Publishers, Inc., 215 4th Ave., New York 3, 1949.

The performance of diagnostic tests in the pediatric age group constitutes a special problem of primary importance. Not only are there manifold technical difficulties, but also the interpretation of results must bear reference to dynamic concepts of growth and development. Further, a large group of test methods is almost exclusively applicable to children and, therefore, is not readily available in standard reference sources. There can be no question of the pressing need for a text which furnishes adequate technical detail, applicability and interpretation of results concerning diagnostic tests in infancy and childhood. Dr. Behrendt has ably compiled a comprehensive discussion of the subject. Of necessity, the basic explanations of the procedures are brief and, at times, incomplete. The sections entitled "Pediatric Considerations" and "Interpretation" are succinct and filled with valuable information.

The volume represents far more than a laboratory manual. Its scope of coverage renders it equally valuable to practicing physicians and to staffs of highly developed pediatric hospitals. It is noteworthy and highly commendable that a twenty-five page section devoted to psychologic testing has been included. In summary, a real contribution has been made in this volume, one which can be appreciated by all physicians concerned with pediatric diagnosis. It is hoped that frequent revision will be possible to keep it a current and excellent reference source.

Maternity in Great Britain: A Survey of Social and Economic Aspects of Pregnancy and Childbirth. By the Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee. Price, $4. Pp. 268, with 47 tables. New York: Oxford University Press, 1948.

This is a carefully worked out survey of maternity problems in Great Britain. The work was done in 1946, therefore just before socialistic control of the medical profession had reached its present height. The mothers of all babies born during a single week of that year were visited. The area covered included England, Wales and Scotland. A total of 13,687 mothers cooperated, of whom 7,287 filled out questionnaires concerning maternity services and the use made of them. This seems to reduce sampling error, as conclusions reached after a survey of small numbers of persons are likely to be inaccurate. A well formulated printed questionnaire was used.

A number of classes of women were interviewed. They were divided into the wives of professional men or salaried workers, of "black coated (white collar)" wage earners, of manual workers, of agricultural workers and of men in other occupations and unmarried mothers. Some interesting figures are given concerning the expenditures for maternity care by persons in these different classes.

In these days, when the possibility of socialized medicine in our country is being discussed, the statement that "few general practitioners have either the time or the interest to undertake domiciliary midwifery except among the most prosperous groups" seems interesting. A large number of deliveries among the low income families are carried out by midwives.

Pain relief seems to be less efficiently attended to than with us. The statement is found that only 52 per cent of those delivered in hospitals were given such relief. Of those delivered at home only 20 per cent were given pain relief.

An interesting section deals with illegitimacy. This increased greatly during the war years, rising in England and Wales from 42 per thousand live births in 1939 to 93 in 1945. There were 680 unmarried mothers included in the figures of this report. The report frankly states that some unwed mothers may have escaped interview. Among them were many young girls, the youngest noted in the report being 15 years of age. No one can go over an honest report dealing with this class of mothers without a conviction that the pseudomoralist, a happily rare type of person with warped mentality who believes that the unmarried mother should be discriminated against and even denied hospital care, is lacking in a sense of social justice.

The pediatrician will find information concerning infant feeding problems among these various classes of mothers. A genuine effort seems to have been made to encourage breast feeding, with success which varied according to many factors, such as crowding in the home, income and the necessity for the mother to work.

The value of breast feeding to the child is emphasized, and the visitors who called on the mothers did what they could to increase the number of breast-fed infants with some success, although not as much as they wished.

The influence of housing and of the frequent inadequacy of living space on both the mother and her infant is amply discussed.

The obstetrician or the pediatrician who desires information of a statistical character concerning parturient women and newborn infants in Great Britain during the immediate postwar years will find much of interest in this little book.

Directory of Pediatric Societies *

INTERNATIONAL

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
Secretary: Dr. H. Zellweger, Kinderklinik, Zurich.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriquez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.
Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

British Paediatric Society

President: Dr. A. G. Maitland-Jones.
Secretary: Dr. Alan Moncrieff, Institute of Child Health, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghi Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

CZECHOSLOVAK PEDIATRIC SOCIETY

Chairman: Prof. Dr. Jiri Brdlik, 2 Sokolská, Prague II.

DANISH PEDIATRIC SOCIETY

Chairman: Prof. Preben Plum.
Secretary: Dr. Elin Fog, Søllingsvey 17, Charlottenlund, Denmark.

GERMAN PEDIATRIC SOCIETY

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).

HELLENIC SOCIETY OF PEDIATRICS

President: Dr. C. Saroglou, Patission St. 74, Athens, Greece.
Secretary-General: Dr. S. Charocopos, Alexandras Ave. 1, Athens, Greece.

INDIAN PEDIATRIC SOCIETY

President: Dr. K. C. Chaudhuri, Dept. of Pediatrics, Medical College, Calcutta.
Secretary: Dr. S. P. Bhattacharjee, Dept. of Pediatrics, Medical College, Calcutta.
Place: Office of the Indian Medical Association, 67 Dharamtala St., Calcutta 13. Time: Every second and fourth Wednesday of each month.

MEDICAL ASSOCIATION OF ISRAEL, NATIONAL PEDIATRIC SOCIETY

President: Prof. L. F. Meyer, 29 Idelson St., Tel-Aviv, Israel.
Secretary: Dr. W. Hirsch, Hadassah Municipal Hospital, Tel-Aviv, Israel.

NEDERLANDSCHE VEREENINGING VOOR KINDERGENEESKUNDE

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

See Medical Association of Israel, National Pediatric Society.

PEDIATRIC SOCIETY OF NEW ZEALAND

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: W. W. Payne.
Secretary: Dr. R. E. Bonham Carter; Dr. I. M. Anderson, 52 Harley St., London.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

SOCIEDAD CHILENA DE PEDIATRIA

President: Dr. Miguel Fabres Izaga.
Secretary-General: Dr. Oscar Undurraga A., Merced 565, Santiago, Chile.
Place: Medical Society, Merced 565, Santiago, Chile. Time: 7 p. m., every Thursday.

SOCIEDAD CUBANA DE PEDIATRIA

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Jaime Jorge, Jose Joaquin Perez, no. 25, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Alberto Peguero, V., Ave. Bolivar 113, P. O. Box, 464, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Roberto L. Sanchez.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Almeida Garrett.
Secretary-Generale: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon.

SOCIEDAD URUGUAYA DE PEDIATRIA

President: Dr. Conrado Pelfort.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Lya Imber Coronil.
Secretary: Dr. Guillermo Tovar, P. O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Paul Letondal, 370 E. Roy St., Montreal, Quebec, Canada.
Secretary-Treasurer: Dr. Edmond Baril, 301 Carré Saint-Louis, App. 1, Montreal, Quebec, Canada.
Time: First and Third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of each month.

SOCIETÉ POLONAISE DE PÉDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. A. Lichtenstein, Crown Princess Louise's Children's Hospital, 30 Polhemsgatan, Stockholm.
Secretary: Dr. K. A. Melin, Färjestadsvägen 16, Ängby.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Prof. C. W. Herlitz, Kungliga Skolöverstyrelsen, Stockholm.
Secretary: Dr. M. d'Avignon, Norrtulls Sjukhus, Stockholm.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm and Pediatric Clinic Upsala. Time: Second Friday of each month (except summer).

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward B. Shaw, 384 Post St., San Francisco 8.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Annual Meeting: Place: Chicago. Time: Oct. 14-19, 1950.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Henry H. Gordon, 4200 E. 9th Ave., Denver 7, Colo.
Secretary-Treasurer: Dr. Robert Ward, Bellevue Hospital, New York 16.
Place: French Lick, Ind. Time: 1950.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Henry E. Gallup.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Time: Four meetings a year.

North Pacific Pediatric Society

President: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.
Secretary-Treasurer: Dr. S. Gorham Babson, 303 Medical Arts Bldg., Portland, Ore.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Joseph Lyday, 227 16th St., Denver 2.
Secretary-Treasurer: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of Denver or the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

Southwestern Pediatric Society

President: Chester I. Mead, 1930 Truxton Ave., Bakersfield, Calif.
Secretary: Dr. Clement H. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.

Arizona Pediatric Society

President: Dr. Carl A. Holmes, 1401 N. 7th Ave., Phoenix.
Secretary-Treasurer: Jacob M. Sobol, 607 Heard Bldg., Phoenix.
Place: Phoenix or Tucson. Time: On call.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Howard J. Morrison, 444 Drayton St., Savannah.
Secretary-Treasurer: Dr. J. Harry Lange, 490 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOICETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 7 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Edward L. Tuohy, Manchester.
Secretary-Treasurer: Dr. William D. Penhale, Concord.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield, N. J.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Jean Craven, 19 W. Third St., Lexington, N. C.
Secretary-Treasurer: Dr. Susan C. Dees, Duke Hospital, Durham, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

NORTH DAKOTA PEDIATRIC SOCIETY

President: Dr. R. E. Dyson, Northwest Clinic, Minot, N. D.
Secretary-Treasurer: Dr. William J. Ball, Northwest Clinic, Minot, N. D.
Place: Fargo Clinic, Fargo, N. D. Time: October 15.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

PHILIPPINE PEDIATRIC SOCIETY

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY

President: Dr. John E. Ashby, 3610 Fairmount, Dallas, Texas.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. Charles H. York, 10465 Carnegie Ave., Cleveland 6.
Secretary: Dr. Earl E. Smith, 10640 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. J. Edmund Bradley, University Hospital, Baltimore 1.
Secretary: Dr. Wilson Grubb, 4 E. 33rd St., Baltimore 18.

BRONX PEDIATRIC SOCIETY

President: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Secretary: Dr. George Weiss, 790 Grand Concourse, New York 51.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Secretary: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn 17.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica, N. Y.
Secretary-Treasurer: Dr. Fred W. Bush, 11 N. Goodman St., Rochester, N. Y.
Place: Various cities in New York. Time: Third Tuesday of April and October.

CENTRAL OHIO PEDIATRIC SOCIETY

President: Dr. E. H. Baxter, 327 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. E. V. Turner, 2479 E. Main St., Columbus, Ohio.
Place: As announced. Time: On call.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Secretary: Dr. Alfred S. Traisman, 6349 N. Clark St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

DALLAS PEDIATRIC SOCIETY

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Wilfred D. H. Nolting, 16840 E. Warren, Detroit.
Secretary: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

FORT WORTH PEDIATRIC SOCIETY

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Rennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

HONOLULU PEDIATRIC SOCIETY

President: Dr. F. D. Nance, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.
Place: At doctors' homes in rotation. Third Thursday of each month, 6 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Jack R. Hild, 3718 Travis St., Houston, Texas.
Secretary: Dr. R. E. Leaton, 3102 San Jacinto, Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Jacob Rosenblum, 161 Rugby Rd., Brooklyn.
Secretary: Dr. Irving Weinstock, 350 Ocean Ave., Brooklyn.
Place: Kings County Medical Society. Time: 8:30 p. m., fourth Monday of October, November, January, March, and April.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N. W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708-15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

President: Dr. Harold T. Vogel, 34-20, 86 St., Jackson Heights, N. Y.
Secretary: Dr. Moe Goldstein 111-32, 76th Ave., Forest Hills, L. I.
Place: Forest Hills, N. Y. Time: Third Monday of October 1950, February and April 1951, and first Monday of December 1950.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. David M. Harris, Medical Arts Bldg., Seattle 1.
Secretary: Dr. William A. Jaquette Jr., 1305 Seneca, Seattle 1.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. F. William Hoehn, 1422 Austin Ave., Waco, Texas.
Secretary: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.
Place: Providence Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

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President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

WICHITA PEDIATRIC SOCIETY

President: Dr. Walter L. Schafer, 401 N. Emporia St., Wichita 2, Kan.
Secretary: Dr. William F. McGuire, 401 N. Emporia St., Wichita 2, Kan.
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Orton, H. B. — Acute Laryngotracheobronchitis. Archives of Otolaryngology. 33:926-960, June 1941.
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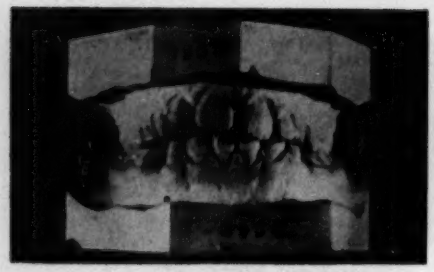

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Ref.: A. Landau, Am. J. Dis. Child., 45: 691, April 1933.

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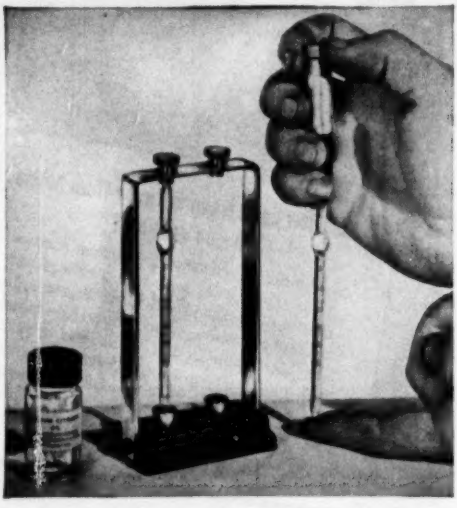

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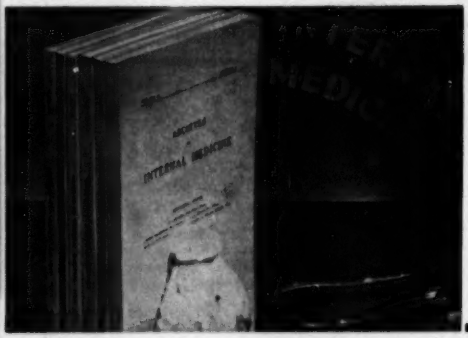

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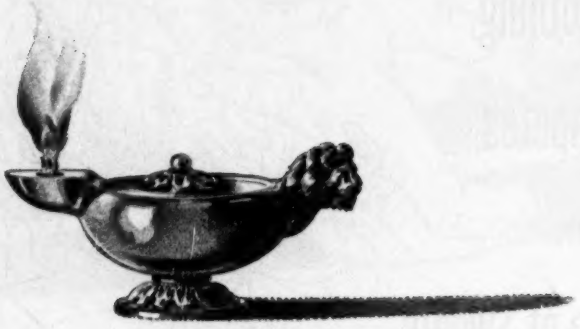

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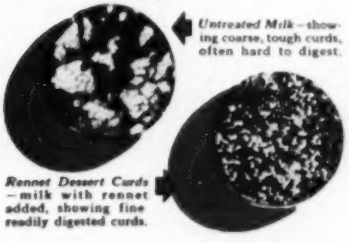

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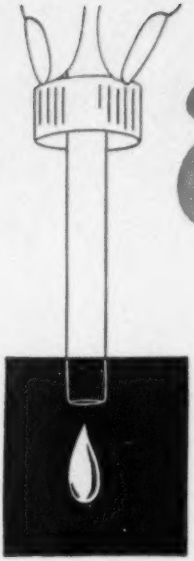

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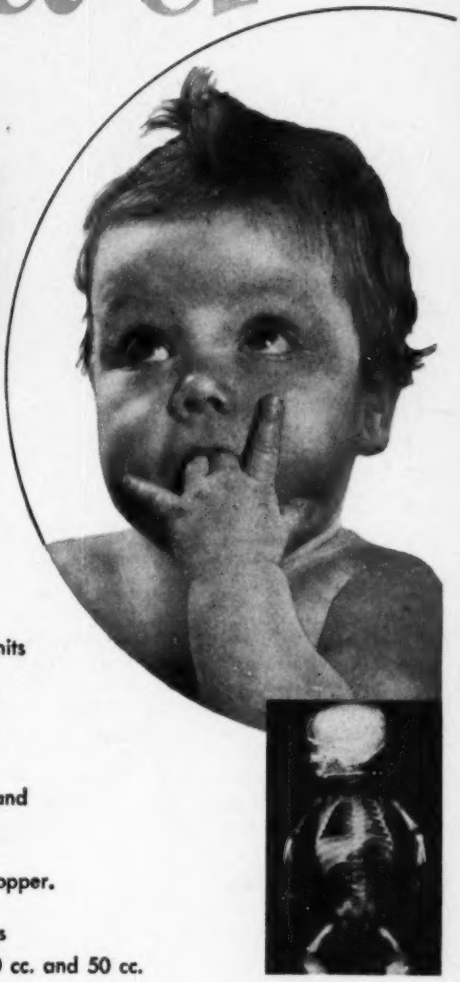

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